EPISEEK™: an In-Depth Market Analysis of Screening High-Risk Lung Cancer Patients

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Table of Contents

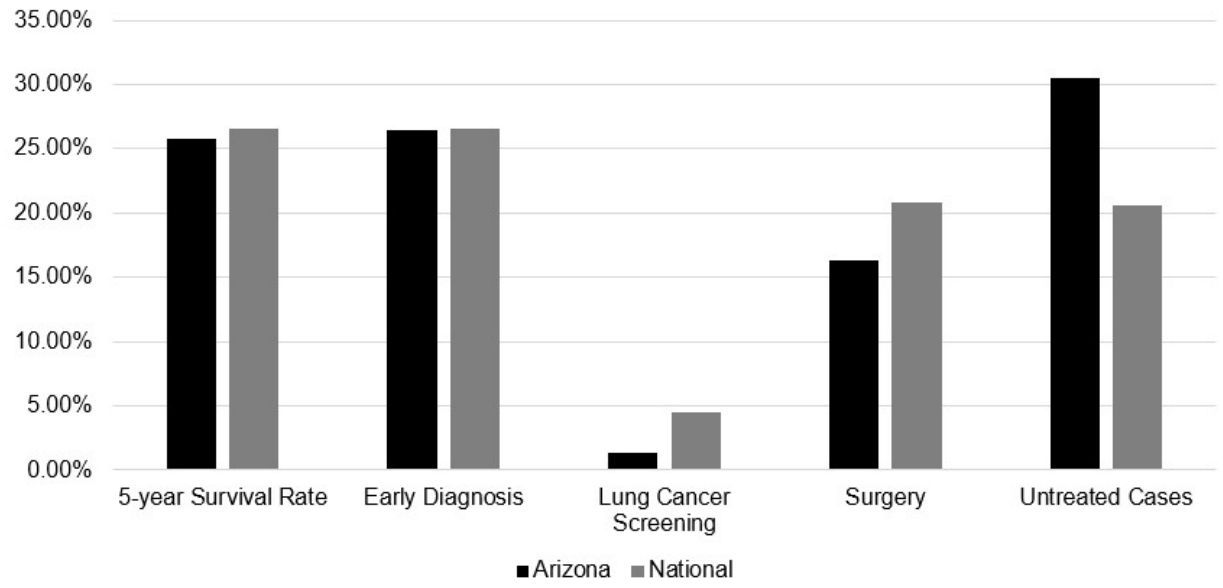
INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the United States, followed by prostate and breast cancers in men and women, respectively. According to the Centers for

Disease Control and Prevention (CDC), the leading cause of lung cancer is cigarette smoking. The development of lung cancer starts with the uncontrolled growth rate of abnormal cells (cancer cells) in the lung (CDC, 2023). There are two common types of lung cancer; non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC) (WHO, 2023).

According to the American Lung Association (ALA), 603,989 people who were diagnosed with lung cancer in 2020, and 55% of them were diagnosed in the last 5 years. Lung cancer accounts for only 11% of new cancer cases, and only 3% of cancer survivors due to its low survival rate. In 2021, there were 134,592 people who died from lung cancer, which is about 22% of all cancer deaths. Among the lung cancer deaths in 2021 about 75% were ages 65 years and older, and 96% were aged 55 years and older. In 2019, the people aged 65 – 74 who died from lung cancer had the highest peak at over 45,000 deaths (ALA, n.d.).

Figure 1 – Arizona Lung Cancer Statistics Compared to National Averages



As shown in **Figure 1**, the lack of treatment in Arizona is notably higher than the national average. There is greater utilization of screening and surgery for lung cancer at the national rate

compared to Arizona's rate. However, both the 5-year survival rate and early diagnosis rates are similar between the national average and Arizona (ALA, 2023).

The goal of low-dose CT (LDCT) screening methods is to minimize patients' exposure to radiation while obtaining quality images for diagnosis. Currently, automated methods are used for pulmonary nodule detection, size measurement, and tissue characterization in LDCT screening. Even with computer assistance, sensitivity for nodule detection typically falls between 80% and 90%, accompanied by a false positive rate ranging from 3 to 8%. This variability indicates that not all cancer cells are detectable, thus recommending the use of nodule detection software as a "second reader" (Gierada et al., 2020).

According to the ALA, patients identified as high-risk can decrease "lung cancer death rate up to 20%" by performing annual LDCT. In 2006, The International Early Lung Cancer Action Program (I-ELCAP) reported that 484 participants diagnosed with a first primary lung cancer through annual screening achieved a 10-year lung cancer-specific survival rate of 80%, with a significant majority having clinical stage I lung cancer (85%) (Henschke et al., 2023). Recent follow-up studies have confirmed the durability of these findings. A 20-year follow-up of the same cohort showed that the 10-year lung cancer-specific survival rate remains robust at 81% (Henschke et al., 2023). Additionally, updated 10-year statistics reaffirmed a consistent 81% survival rate for all participants (Henschke et al., 2023).

In 2021, following the ALA guidelines, patients considered high risk for lung cancer are those aged 50 to 80 years with a smoking history of 20 or more pack years (equivalent to smoking 1 pack a day for 20 years, 2 packs a day for 10 years, etc.). Their smoking status is either current smokers or individuals who quit within the last 15 years (ALA, 2023). Based on the data, there are "approximately 14.2 million people are eligible for screening" (Poon et al., 2023).

Table 1

Stage	5-Year Overall Survival Rate (%)	5-Year Lung Cancer-Specific Survival Rate (%)

I	76.9	82.3
II	56.1	59.7
III	32.6	37.2
IV	21.4	26.4

As shown in **Table 1**, early detection significantly improves the chances of patient survival compared to detection at advanced stages of the disease (He et al., 2022). The survival rate was not explained to the patients in terms of how long they would live; rather, the data provided indicates the survival rate of individuals after undergoing treatment following diagnosis (American Cancer Society, 2024).

For most patients, no preparation is needed before lung cancer screening unless specified by the service provider or if the patients are unwell. Before scanning, patients must change into a gown, although sometimes they are allowed to keep their clothes. In addition to changing into a gown, patients must remove all jewelry, watches, or any items made of metal. Then, patients will lie on a table outside the CT scanner. The scanning process takes only a few minutes, and patients do not need injections or sedatives. The machine, which is large and donut-shaped, will circle the patients to take pictures of the lungs from different angles. The technician will guide patients through the process, with the primary requirement being that patients remain still (Cleveland Clinic, 2021).

Outside of the clinical trial setting, the efficiency of LDCT screening has yet to be proven. Factors contributing to the low implementation of LDCT in routine check-ups include patients' fear, stigma, and concerns about the cost of screening. To prove its effectiveness, LDCT screening needs to be conducted on a larger scale. In 2016, it was estimated that less than 2% of the 7.6 million eligible individuals were screened in the United States and 14% of those eligible across 10 states in 2017 (Gierada et al., 2020).

Liquid Biopsy and Cancer Biomarkers

Liquid biopsy (LB), which involves testing of body fluids such as blood, urine, cerebrospinal fluid, and saliva for cancer diagnosis is mainly focused on the detection of particular biomarkers. LB is defined by the National Cancer Institute (NCI) as a blood test that examines the presence of circulating tumor cells (CTCs) or Deoxyribonucleic acid (DNA) from these cells in the circulation. Other definitions emphasize detecting cancerous constituents within blood samples (Connal et al., 2023).

Although cancer is a systemic disease, not all biomarkers are directly linked to cancer cells. At early stages, tumors release small amounts of tumor-related biomarkers into the bloodstream making them challenging to detect. Conversely, others, such as immune response derived non-tumor related markers, are highly prevalent. This could lead to early detection of cancer through a pan-omics analysis that combines tumor-derived signals with non-tumorous ones (Connal et al., 2023). Liquid biopsies confer several advantages over traditional surgical tissue biopsies, including lower invasiveness and risk, lower procedural costs, and greater potential for comprehensive genomic, proteomic, and metabolomic information. Nevertheless, even though they have these advantages over traditional methods such as tissue biopsies, LB are yet to be included routinely among diagnostic modalities for malignancies like cancers since they lack sensitivity and specificity compared to tissue biopsies, which have very low rates of false positives (Connal et al., 2023).

EPISEEK

Precision Epigenomics (P.E.) focuses on advanced molecular diagnostics, which is aimed at enhancing cancer patient care through accurate diagnosis and effective treatment management. They perform cost-effective clinical laboratory tests that detect abnormal DNA

methylation using various sample types such as peripheral blood, body fluids, and tissue biopsies of different origins. Recently, they have developed EPISEEK™, a state-of-the-art multi-cancer early detection (MCED) test based on standard blood samples (P.E., 2023).

In 2023, P.E. received a patent for EPISEEK™, which uses its own DNA methylation biomarkers for diagnosing and monitoring different forms of cancer. This technology utilizes LB to avoid invasive surgical procedures by providing important details about tumor type, and disease progression as well as best treatment options. When cell-free DNA (cfDNA) specific to cancer is examined by EPISEEK™ the invention accurately detects cancer before conventional imaging procedures and offers greater access than traditional tissue biopsies (P.E., 2023).

Methylated DNA

DNA methylation is one of the most vital epigenetic changes that involves the addition of a methyl group to a cytosine, which regulates gene expression by either attracting repressors or blocking transcription factors. During development, the patterns undergo dynamic changes in methylation leading to stable gene transcription in differentiated cells found in specific tissues (Nishiyama & Nakanishi, 2021).

In cancer, disturbances in DNA methylation are evidenced through global hypomethylation throughout the genome and hypermethylation at CpG islands related to tumor suppressor genes and developmental regulators. These DNA methyltransferases are usually dormant but are regulated through particular histone modifications at their methylating places (Nishiyama & Nakanishi, 2021).

Carcinogenesis progressively modifies DNA methylation patterns such that partially methylated domains (PMDs) as well as solo-W-Cytosine-Guanine-W (W: A/T (adenine or thymine)) sequences experience hypomethylation while promoters with low gene expression undergo hypermethylation thereby ensuring a stable repression of genes. It turns out that the

previously held belief that DNA methylation is an abnormality that promotes oncogenesis by silencing tumor suppressor genes (TSGs) was wrong (Nishiyama & Nakanishi, 2021). This indicates that comprehending DNA methylation abnormalities in cancer is an important step in developing new cancer therapies and also highlights the importance of epigenetic regulation in health and disease.

METHODS

Clinical Analysis

To execute a clinical analysis of LDCT for lung cancer screening in high-risk patients, a literature review of peer reviewed journal articles was performed. Peer reviewed journal articles were obtained through the ASU Library, the National Library of Medicine, PubMed and Google Scholar. The literature review produced data points to measure the sensitivity, specificity, false positive rates and false negative rates associated with LDCT screening for lung cancer, identifiable causes of inconsistencies in data, recommendations for diagnostic workup and treatment for lung cancer and weaknesses of the LDCT technology as a lung cancer screening method. Data obtained through literature review was cross referenced with other peer reviewed journals, reputable sites, databases and widely recognized randomized trials. The reputable sites consulted for this report include the National Cancer Institute/National Institutes of Health (NIH), Veterans Health Administration, American Cancer Society, Mayo Clinic, American Lung Association, Cleveland Clinic, United States Preventative Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS). Databases such as the Cancer Data Access System (CDAS) and Surveillance, Epidemiology and End Results (SEER) were used to access data and

information that was readily available to the public. The nationally recognized trials referenced include The National Lung Screening Trial (NLST), The Nederlands-Leuvens Longkanker Screenings Onderzoek Trial (NELSON) and The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO). Articles are meta data analysis of studies associated with LDCT lung cancer screening that fall outside the trials listed above. Literature and data included were selected with the parameters that the technology (i.e. LDCT and CAD systems) were used to screen for lung cancer and that the screening was conducted on patients identified as being at high-risk for developing lung cancer.

Cost Analyses:

In order to review the economic burden of lung cancer and cost-effectiveness of LDCT in the current market, a literature review of multiple (large) clinical data sets enhances the depth of this analysis. Databases including SEER-Medicare, I-ELCAP, Optum's Integrated Claims, and NLST provide retrospective evidence to support comprehensive understanding of the landscape and theoretical discussion for the future market. This approach also highlights gaps in the existing market, paving the way for future research.

The SEER–Medicare database integrates two extensive population-based datasets: SEER cancer registry data and Medicare enrollment and claims files (Apple et al., 2023). SEER covers around 35% of the U.S. population, gathering information on newly diagnosed cancer cases including initial treatment, demographics, and disease characteristics (Apple et al., 2023). The dataset includes claims for covered healthcare services, such as hospital stays, outpatient visits, home healthcare, and hospice services for patients enrolled in Medicare (Apple et al., 2023). Approximately 95% of elderly SEER patients are linked to their Medicare data (Apple et al., 2023).

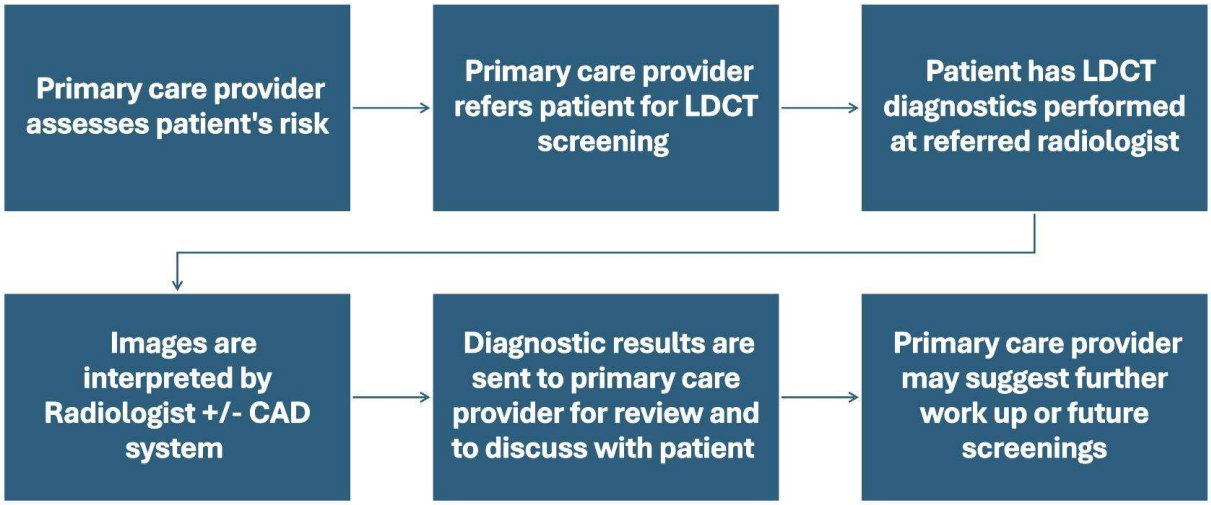
Cost analyses comparing LDCT to EPISEEK to no-screen were conducted using retrospective studies on NLST data, cost efficacy models examining the use of multi-cancer early detection (MCED) tests for cancer screening, and a qualitative review of current lung cancer screening methods to assess for potential advantages of EPISEEK over LDCT or no-screen.

RESULTS

Background on LDCT Screening Method:

Low dose computed tomography (LDCT) scans are the current standard for lung cancer screening in high-risk patients. LDCTs are recommended by primary care physicians upon assessment of a patient's health history and lifestyle, and with the completion of a physical exam. If a patient's primary care provider deems them high risk, they will be referred for lung cancer screening with LDCT scan by a radiologist. The high-risk patient will have imaging performed at a radiology facility where specialized equipment and staff can obtain and interpret the necessary imaging. The results are then sent back to the primary care physician, who will create an appropriate treatment plan based on the LDCT screening results (American Lung Association, 2024).

Figure 2 - Routine Workflow for LDCT Screening for Patients at High Risk for Developing Lung Cancer



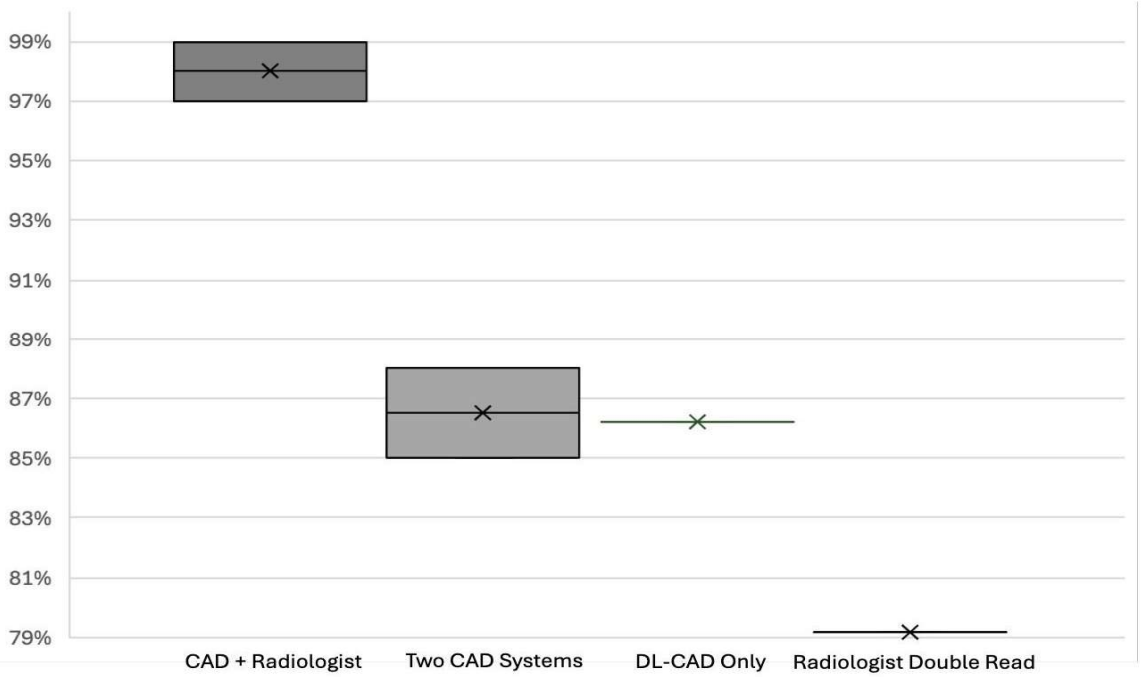
(American Lung Association, 2024)

Lung cancer is detected with LDCT through the identification and classification of lung nodules on chest imaging. Lung nodules are identified and deemed to be positive or negative for cancer screening based on a combination of factors including the size of the nodule, the composition of the nodule, the location of the nodule within the lungs and whether the nodule is new or growing. The American College of Radiology's Lung-RADs criteria is a widely accepted guide in the United States for accessing lung nodules. This criterion describes a nodule as suspicious for cancer when it is between 4 mm to 8 mm in size. The size of the nodule is evaluated in conjunction with the nodule's composition, and if it is new or growing (American College of Radiology, 2022). The composition of lung nodules can be defined as solid nodules, ground-glass nodules or part solid nodules (Li et al., 2018). The ability to accurately identify and classify lung nodules on LDCT images is the crux of quality LDCT screening for lung cancer in high-risk patients.

Sensitivity and Specificity of LDCT

Sensitivity of LDCT screening for lung cancer has been reported to fall between 59-100% with most studies reporting a sensitivity of greater than 80% (Jonas et al., 2021). When evaluating the sensitivity of LDCT screening through various interpretation methods, the range of sensitivity can be appreciated more comprehensively. When LDCT lung cancer screening images are interpreted by a radiologist with a computer-aided diagnostic (CAD) system implemented as a secondary interpretation tool to the radiologist, sensitivity has been noted to fall into a smaller, more desirable range of 97-99% (Lancaster et al., 2022). In cases where no CAD system was utilized, and a radiologist double read interpretation method was applied, sensitivity fell to 79.2% (Li et al., 2018). Sensitivity without a radiologist utilized for image interpretation has also been explored. Utilizing two CAD systems or one deep learning-based CAD (DL-CAD) system produced sensitivities of 85-88% and 86.2% respectively (Lancaster et al., 2022; Li et al., 2018).

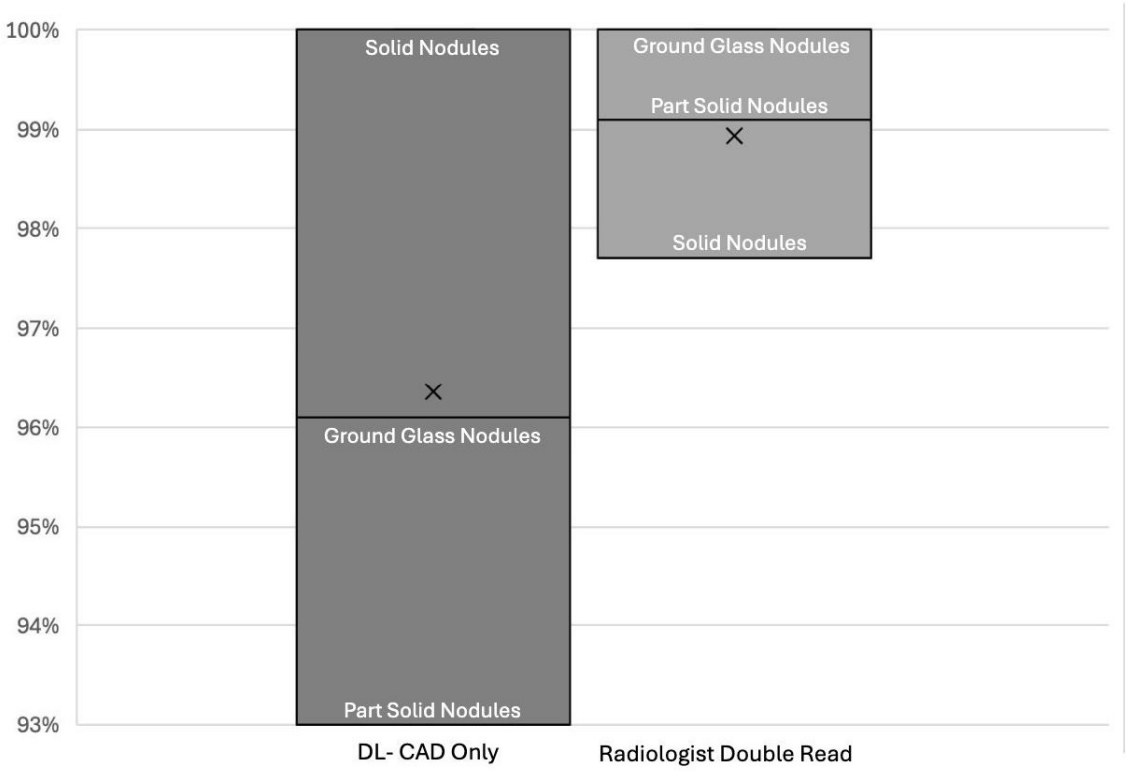
Figure 3- Sensitivity of LDCT Screening With Various Interpretation Methods



(Jonas et al, 2021; Lancaster et al, 2022; Li et al, 2018)

Specificity of LDCT screening for lung cancer also has a significant range, with specificity reported anywhere from 26.4-99.7%; most studies reported a specificity of greater than 75% (Jonas et al., 2021). Specificity variation between interpretation methods has been noted to be significant when evaluating the accuracy of classifying lung nodule characteristics. Specificity for radiologist double read and single DL-CAD system for nodule characteristic interpretation methods are 99.1-100% and 93-100% respectively (Li et al., 2018).

Figure 4 - Specificity of LDCT Screening With Various Interpretation Methods



(Jonas et al, 2021; Li et al, 2018)

The variability in sensitivity and specificity of LDCT can be attributed to several factors. These factors include human error, the use or not of computer-aid diagnostic (CAD) systems, varying quality of imaging due to different CT technology being utilized between facilities, ability to correctly classify lung nodule characteristics and the set parameters that constitute a positive or negative screening result.

Human error is noted to affect the accuracy of LDCT imaging results as it contributes to variability in interpretation accuracy. Because each radiologist has a unique educational and work experience, the ability for accurate interpretation of LDCT lung images may be varied among radiologists within the field. This variability in skill will subsequently lead to varying sensitivity and specificity of LDCT scans as false negatives and false positive results will occur secondary to interpretation errors. Depending on the quality of a radiologist's education, training

and their tenure in the field, some physicians may be more accurate in their interpretations than others. Workload fatigue is also a significant contributing factor to radiologist interpretation error; the push for lung cancer screening for high-risk patients has led to a significant caseload increase for radiologists. This increase in cases has resulted in the over taxation of the radiologist workforce. The quality of interpretation may suffer in the face of overwhelming pressure to increase the quantity of images processed per radiologist. Also, identification and classification of lung nodules can be nuanced and slightly subjective and because of this, and the above stated factors, radiologists can be prone to errors.

To account for human error, many radiology facilities have adopted CAD systems to act as a secondary interpreter of LDCT scans. While these systems can be beneficial for helping to improve sensitivity and specificity of LDCT scans, it is unclear how prevalent these systems are within the field. Because the use of a CAD system as a secondary interpreter to a radiologist is not required, its mandated implementation has yet to be considered standard of care and thus is not standardized across radiologic facilities. It is due to this assumption that not all facilities implement CAD systems in the interpretation of LDCT images, that leads to another identifiable factor that contributes to the large range within the sensitivity and specificity of LDCT scans. Not only is it variable whether a CAD system is used or not, but the quality of the system can also affect the accuracy of its identification and classification of lung nodules. The complexity of a CAD system based on its algorithm and deep learning capabilities can affect the accuracy of lung nodule identification and classification. It should be noted that many CAD systems have been observed to misclassify lung nodule characteristics; heterogeneity of lung nodules has led CAD systems to misinterpret the characteristics of the tumors (Li et al., 2018).

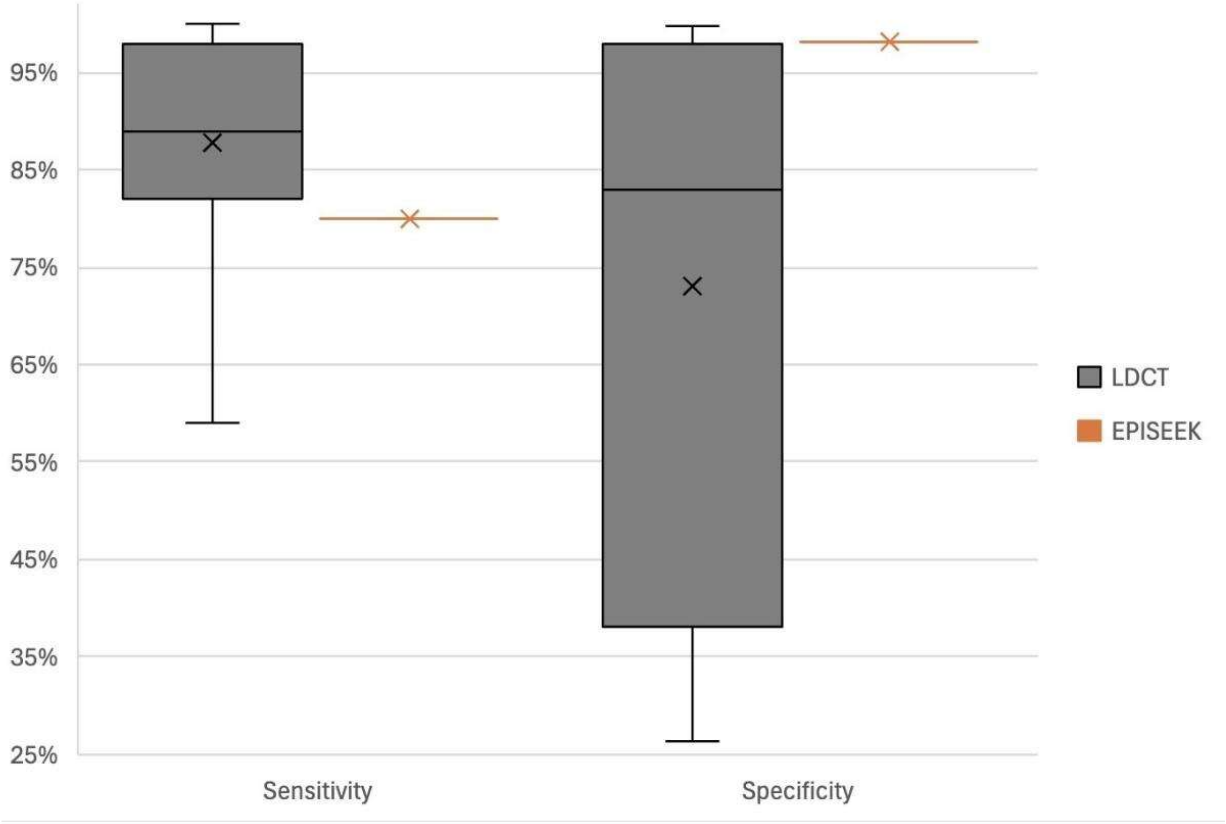
Along with CAD system quality, another contributing factor to LDCT sensitivity and specificity could be due to varying quality of CT machines within different facilities. Facilities without the means to financially budget for more modern CT machines, may be working with

images of lower quality than more modern CT technology. This is in part due to the thickness of the image slices. Thinner slices will be able to detect more nodules and smaller sized nodules than thicker image slices (National Cancer Institute, 2024). Due to this, interpretation by radiologists and/or CAD systems may suffer due to poor quality images.

Lastly, the parameters that determine the definition of positive versus negative can greatly affect the sensitivity and specificity of LDCT scans. An attempt to standardize the definition of a positive screening result through evaluating the size, classification and the state of growth of a nodule has been implemented by the American College of Radiology but is not always recognized as standard outside of the United States, nor is it utilized within all randomized trials for their methods of interpretation. Definitions of positive interpretations that are set too broadly or too conservatively will result in varying degrees of sensitivity and specificity (Guo et al., 2023), thus leading to inconsistencies within the literature regarding sensitivity and specificity of LDCT scans.

The sensitivity and specificity of the LDCT screening method can help us better understand the false positive and false negative rates of this diagnostic screening tool, which will provide context for the potential harms to screening patients. These values can also help when measuring one diagnostic tool against another to compare and contrast clinical validity. An example of this is seen in figure 4 where sensitivity and specificity of the LDCT screening diagnostic tool is compared to the EPISEEK diagnostic tool.

Figure 5 - Sensitivity and Specificity of LDCT vs. EPISEEK



(Jonas et al, 2021; Lancaster et al, 2022; Li et al, 2018)

False Positive and False Negative Rates

False positive rates of LDCT lung cancer screening have been noted to range between 7.9-49.3%. The NLST study noted a false positive rate at baseline screening to be 26.3% while the NELSON study noted baseline false positive rate at 19.8%. The Veterans Health Administration had varied results with a range of 12.6 to 45.8% as their false positive rate; average 28.9%. A study conducted that employed 112 radiologists from 32 screening centers to read over 100 radiographic images noted a mean false positive rate of 28.7% and a range of 3.8-69% (Jonas et al., 2021).

False positive results can be secondary to human and/or technological error that leads to either the overdiagnosis of cancers or the identification of incidental health findings unrelated to lung cancer as cancer. Studies have noted that 20 to 60% of false positives results in current and former smokers have been secondary to incidental findings such as inflamed tissue masses (e.g. benign lymph nodes or granulomata), lung scarring, and other noncancerous conditions peripherally associated with smoking. Misdiagnosis of incidental findings as cancer in patients with underlying lung disease such as tuberculosis, emphysema or fibrosis is also common at 87% (Wood et al., 2018). Overdiagnosis– diagnosis of tumors that are non-life threatening/will not be the cause of death in the patient, was reported for 18% of the lung cancers detected with LDCT in the NLST study (*National Lung Screening Trial,* 2014).

In both instances of false positives results, detriments to the patient's health and wellbeing are possible due to harms that can occur as result of unnecessary and risky follow-up diagnostics or treatment. Not only does this create an economic burden due to costs associated with the additional tests (e.g. materials, staff, equipment, etc...), but the potential harm caused to patients by unnecessary diagnostics could lead to malpractice lawsuits.

Figure 6 - False Positive Harms

- **Unnecessary procedures and treatment for the patient.**

Procedure: Transthoracic Biopsy

Risk: 20% chance of lung collapse or pneumothorax.

Procedure: Bronchoscopy Biopsy

Risk: lung collapse or pneumothorax (less likely than with transthoracic method).

Procedure: Wedge Resection

Risk: Adverse reactions secondary to general anesthesia (i.e. allergic reaction, hypothermia, hypotension, death, etc...).

Procedure: Surgical Excision of Cancer

Risk: Complications secondary to surgery (i.e. Infection, excessive bleeding, death, etc...).

Treatment: Chemotherapy

Side Effects: Hair loss, nausea and vomiting, reduced appetite and weight loss, mouth sores, constipation or diarrhea, fatigue, increased risk of infection and easy bleeding or bruising.

Treatment: Immunotherapy

Side Effects: Fatigue, cough, nausea, itching, skin rash, loss of appetite, stomach pain, constipation or diarrhea, joint, muscle or bone pain.

Treatment: Radiation Therapy

Side Effects: General weakness and fatigue, dry, red, itchy or peeling skin, shortness of breath, swallowing difficulties, sore throat, shoulder stiffness, radiation pneumonitis (coughing, fever and a sensation of fullness in the chest that can occur several weeks or months after radiation therapy), radiation fibrosis (lung scarring).

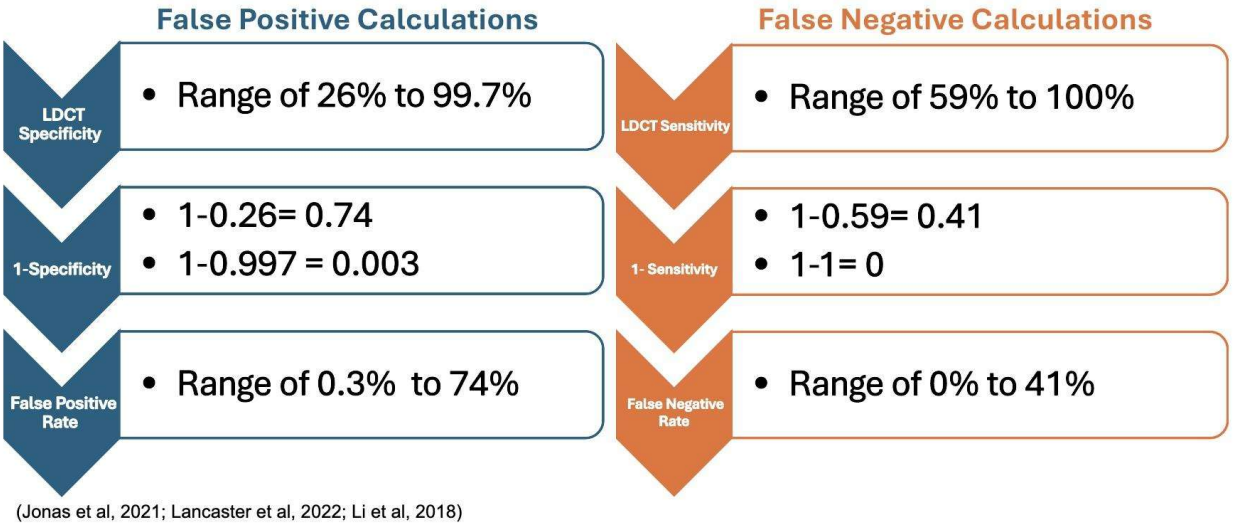
(Bixby, 2024; Moffitt Cancer Center, 2024)

False negative rates for LDCT screening are not as widely reported, with few sources having this data available for review. One study evaluating the performance of LDCT screening for lung cancer screening over the course of a five-year period reported a false negative rate of 8%, while the NY-Early Lung Cancer Action Project (NY-ELCAP) reported a slightly higher false negative rate of 10% (Veronesi et al., 2014). Without further study of the false negative rate, it is difficult to appreciate its true value, but it is suggested that LDCT screening false negative rates could be as high as 15% (Bartlett et al., 2021; Shabpiray et al., 2024).

False negative results are also secondary to human and/or technological errors that lead to lung cancers being missed completely or lung nodules being underrecognized (Veronesi et al., 2014). There is a 30% chance that a radiologist will completely miss detecting nodules on imaging (Doi, 2007). In the NLST study, 40 cases were later deemed to have positive results with follow up CT screening, with 35% of these cases identified as having initial false negative results due to nodules being misinterpreted and 10% being deemed insignificant due to the small size of the nodules (Bartlett et al., 2021).

False negatives for lung cancer screening presents a significant risk to patients as it delays treatment for lung cancer, often leaving cancers to grow unchecked to progress into a later stage cancer. As later stage lung cancer is more difficult to treat, patient prognosis in the face of false negative screening results can be very poor and the economic burden for treatment is significantly increased due to the aggressive measures needed regarding treatment.

Figure 7 - LDCT False Positive and False Negative Calculations



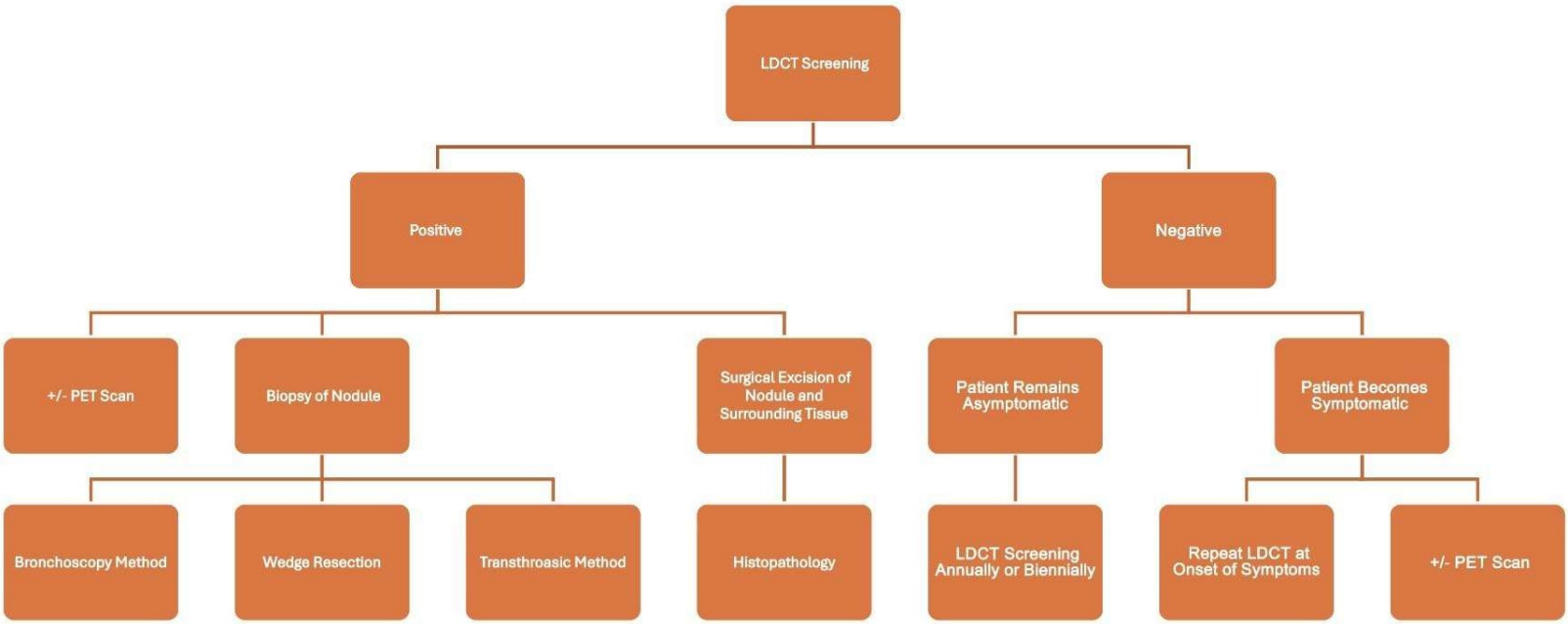
(Jonas et al, 2021; Lancaster et al, 2022; Li et al, 2018)

Work-up and Treatment With LDCT or No Screening

Method

If the LDCT screening method is employed on asymptomatic high-risk patients, they will likely be diagnosed with lung cancer at an early stage of the disease, leading to better prognosis and more economically efficient outcome. Follow up after LDCT screening allows for a definitive diagnosis of lung cancer as well as allows for the staging of the disease. If no nodules are detected during screening and the patient remains asymptomatic, LDCT screenings will be recommended annually or biennially. If nodules are detected, low concern nodules may result in

Figure 8 - Post LDCT Screening Diagnostic Workflow



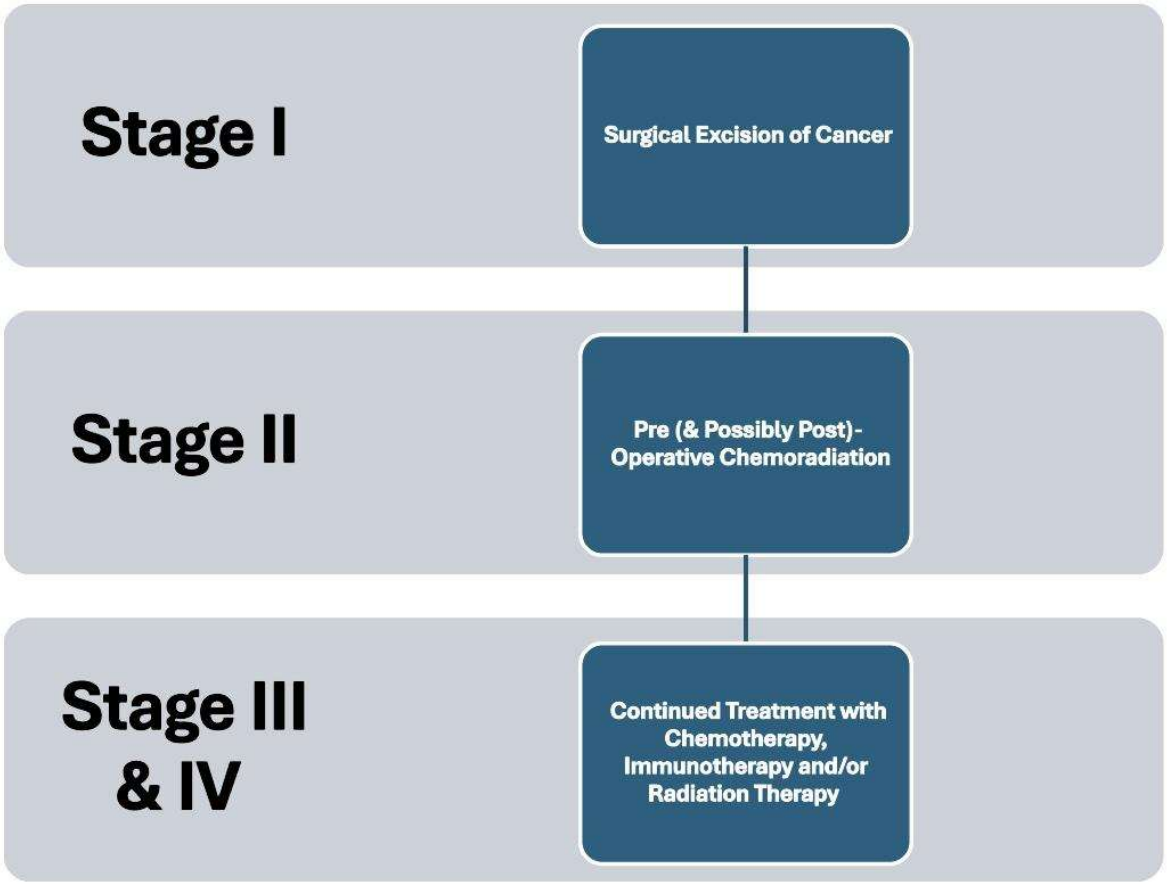
(Bixby, 2024; *Follow-up after screening,* 2023)

follow up imaging via additional LDCT or PET/CT scan sooner than 12 months. If nodules detected are of high concern, then a biopsy or surgical removal and histopathology of the nodule will be recommended to confirm and stage the cancer (*Follow-up after screening,* 2023). Once confirmation and staging of cancer has been achieved, treatment options will be more efficiently and accurately determined by the patient's provider. Stage 0 to stage II NSCLC treatment can include varying options such as surgical resection of the tumor, chemotherapy, immunotherapy, targeted therapy and/or radiation therapy. Often a combination of these therapies is employed to combat the disease (*Non-small cell lung cancer treatment,* 2024).

If no lung cancer screening methods are employed on high-risk patients, they may be diagnosed at the onset of symptoms. Generally, when a patient becomes symptomatic, lung cancer has progressed into the later stages (stage III & IV) and will be much more difficult to treat and has a poor prognosis. Confirmation and treatment of late-stage cancer will be

achieved by the same methods as those of the LDCT screening methods, but will be implemented on a more aggressive level.

Figure 9 - Treatment Recommendations Post Diagnostic Work up



(Bixby, 2024; *Non-small cell lung cancer treatment,* 2024)

Gaps in LDCT Lung Cancer Screening Method Lending to Poor Screening Rates

Lung cancer screening compliance is low due to several factors, and both the patient and provider perspective can hold clues to why this is so. The patient's perception of the screening process can greatly affect the compliance for screening. There are many patient-perceived barriers to screening via the LDCT method, including lack of knowledge by patients of lung cancer screening recommendations (Bixby, 2024), the inconvenience of the LDCT process (e.g. transportation issues, returning for a separate appointment with a new provider, undressing and redressing into a hospital gown, lack of time to dedicate to testing, etc..), fear of LDCT (e.g. claustrophobia and/or radiation exposure), LDCT associated false positive and false negatives rates, which can cause mistrust of or anxiety over the screening results, and lastly, concern for the possible lack of insurance coverage for screening diagnostics (Coughlin et al., 2020; CT scan and Claustrophobia, 2022).

When considering the provider's perspective, LDCT screening compliance can be due to challenges associated with the lung cancer screening system and the implementation of LDCT screening. According to Interventional Pulmonologist, Dr. Billie Bixby, the third-party paying systems can cause significant barriers to screening compliance as the need for lung cancer screening must be thoroughly documented to prove the need to CMS to ensure Medicaid coverage of the LDCT screening diagnostics. This documentation process is time intensive and requires verification of compliance by additional staff to ensure it is properly completed prior to submission to CMS (2024). Implementation challenges also arise due to poor electronic medical record (EMR) systems resulting in physicians not being notified of patients meeting screening criteria, lack of provider knowledge (i.e. screening guidelines, results interpretation, follow-up

and/or referral protocol, etc..), provider time constraints and/or LDCT equipment malfunction leading to the inability to even obtain screening images (Bixby, 2024; Coughlin et al., 2020).

Clinical Analysis of EPISEEK

DNA methylation status may be a useful prognostic marker for detecting recurrence. Changes in the methylation status have been both identified and described in robust longitudinal studies. DNA methylation biomarkers including: NORG, BMP3, VIM, and SHOX2 have been identified and adopted for use in diagnostics; IGFBP-3, APC, p16, CDH13, and RASSFIA have been utilized as prognostic indicators.

Common mutations in the development and progression of NSCLC that can be exploited as biomarkers in testing include: Epidermal Growth Factor (EGFR), KRAS, and anaplastic lymphoma kinase. (ALK), and p16. Biomarkers confer several dynamic advantages. First, they provide a lead-time over clinical diagnosis. Second, they are highly sensitive to avoid false negative results. Finally, they are highly specific as to avoid false positive results.

Precision Epigenomics EPISEEK is a MCED screening test that is capable of identifying more than 20 prevalent cancer types, many of which have no other early detection tests available. The EPISEEK liquid biopsy is intended to be used as a complementary tool to established cancer screening assessments (TruDiagnostic, 2024). It is significant to note that these screening tests do not diagnose cancer; they are otherwise designed to detect possible cancer in asymptomatic healthy populations. This assay can detect those cancers that are clandestine and notoriously difficult to detect. This test analyzes epigenetic modifications present in cfDNA, specifically DNA methylation patterns. It does not screen for hereditary risk of developing malignancy; it is however, designed to detect the presence of malignancy. It is recommended for use in adults 45 years and older and patients younger with elevated risk factors that could potentially benefit. On the other hand, it is not recommended for those

individuals under 21, pregnant women, those with active known malignancies, or those individuals currently being treated for cancer.

EPISEEK detects the most prevalent lethal solid tumors including: lung cancer, breast cancer, prostate cancer, colorectal cancer, neck cancer, urinary bladder cancer, and esophageal cancer. Further bioinformatic analysis showed the loci have increased sensitivity and specificity for cervical squamous cell carcinoma, diffuse large B-cell lymphoma, glioma, liver hepatocellular carcinoma, mesothelioma, gastric adenocarcinoma, uterine endometrial carcinoma, and uterine carcinosarcoma (TruDiagnostic, 2024).

Specimens for EPISEEK consist of a peripheral whole blood sample – 10 milliliters each submitted in the two Streck Cell-Free DNA tubes. The patient does not need to be fasting for this assay. The specimens must not be frozen, and should be stored and transported at 37-87 F. Those specimens that are hemolyzed, clotted, of insufficient quantity, in expired tubes, not properly labeled with 2 unique identifiers, not included with complete documents, submitted in tubes other than those provided, and/or not received within 48 hours of being collected will be rejected.

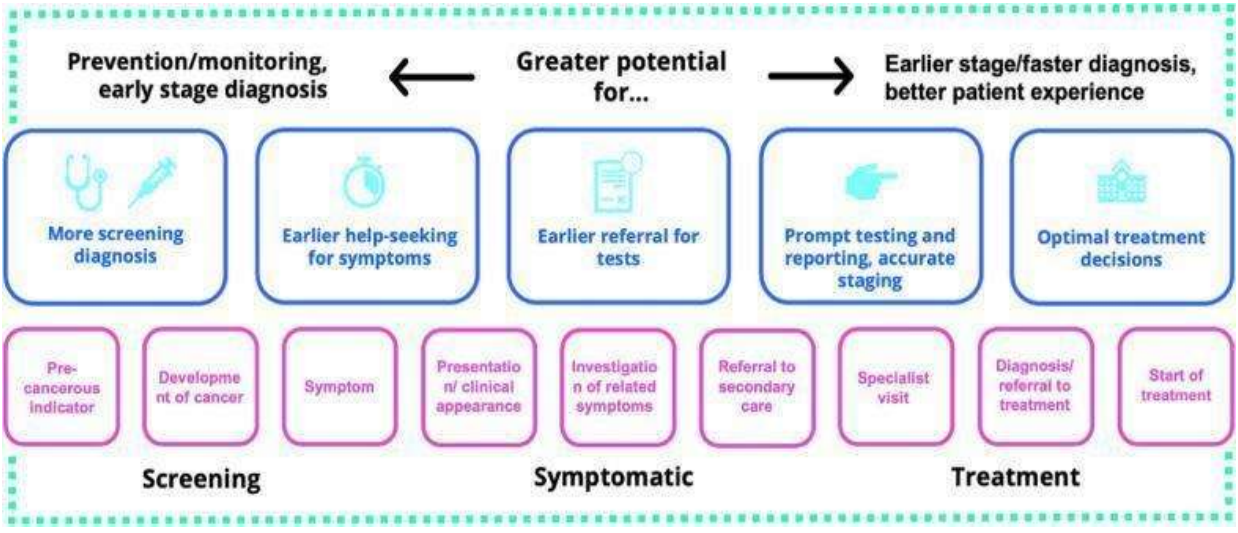
Liquid biopsies (LBs) test blood samples to look for cancer cells from a tumor that are circulating in the blood, or for pieces of DNA from tumor cells that are in the blood (Honore, 2021). LBs like EPISEEK, have set themselves apart competitively in the market from other technologies due to: ease of use in tumor sampling, continuous monitoring by repeated sampling, devising personalized therapeutic regimens, screening for therapeutic resistance, and monitoring and executing surveillance for MRD. LBs can interrogate clonally divergent, distant lesions without sampling bias, thus allowing longitudinal monitoring of patients during treatment. Specifically, EPISEEK detects 10 proprietary biomarkers in their assay.

EPISEEK's methodology includes quantitative (qPCR), a multiplex reaction, and proprietary software that is utilized in the analysis of outputs. This robust platform's workflow begins with the blood specimen being spun down to plasma to yield 2 ml aliquots. Next, the cfDNA is isolated and purified with proteinase and SDS on the King Fisher or manually. Proteinase K is a serine protease that degrades proteins by hydrolyzing peptide bonds. It is useful in removing nucleases that can degrade both DNA and RNA, as well as, in the isolation of intact genomic DNA from various sources. Due to its stability in a wide range of pH and temperatures, and the fact that it can withstand many detergents and denaturing agents, it is ideal for sample preparation. The next step is bisulfite modification of the DNA and a clean-up on the King Fisher. Bisulfite modification, also known as bisulfite conversion, is one of the most useful tools for analyzing methylation of cytosine residues at position 5. Treatment of DNA with bisulfite (sulphonation) leads to the deamination of cytosine residues and converts them to uracil while 5-methylcytosine residues remain the same. This technique allows a technologist to determine the sample's unique methylation pattern. The preamp and amplification is a two-step qPCR reaction that was adopted as the principal analytical strategy. In the first step the methylated DNA template is pre-amplified in a multiplex reaction testing a cocktail of all primer pairs. The product from the first step is then diluted and used in individual standard qPCR reactions to quantify the individual markers. Lastly, outputs are analyzed using proprietary software.

Results of EPISEEK are presented as: "Cancer Signal Not Detected," 'Indeterminate Signal Detected," or "Abnormal Signal Detected." A "Cancer Signal Not Detected: result does not completely rule out the presence of cancer. The workup report states one should continue with all standard of care screening options at intervals that are appropriate. An "Indeterminate Signal Detected" would indicate more false positives present. This workup would recommend additional follow-ups. An "Abnormal Signal Detected" is indicative of more tests needed. An

evaluation is warranted including a detailed history and physical with special attention to risk factors, as well as, PET/CT imaging and additional diagnostic tests recommended.

LBs analyze cfDNA, whereas standard biopsies analyze genomic DNA. CfDNA is shed into the bloodstream via necrosis, apoptosis, or active secretion. DNA shed by tumor cells is physically more fragmented than healthy cfDNA. In normal cells there are approximately 166 base pairs (bp) versus 143 bp in cancer cells (Graham, n.d). A tissue biopsy can be compared to a 'snapshot' of the cancer, whereas the analysis of circulating tumor DNA is a 'screenshot' of the primary and metastatic tumor and longitudinal liquid biopsies can be viewed as a 'motion picture' of tumor evolution (Murtaza, 2015).The collection procedure of LB is simplistic, not time-consuming (outpatient care), and minimally invasive via a blood sample, whereas, standard biopsy procedures are invasive, time-consuming (hospitalization may be required), and tissue intensive. LBs reveal a comprehensive tissue profile, whereas standard biopsies unveil only a localized sampling of tissue. With LBs one could undergo repeated sampling throughout treatment versus standard biopsies an individual cannot due to high risk and pain thresholds. In addition, with LBs there is no histological evaluating that needs to be performed subsequent to the test as in standard biopsies which require a trained histologist or pathologist to examine and result the specimen.

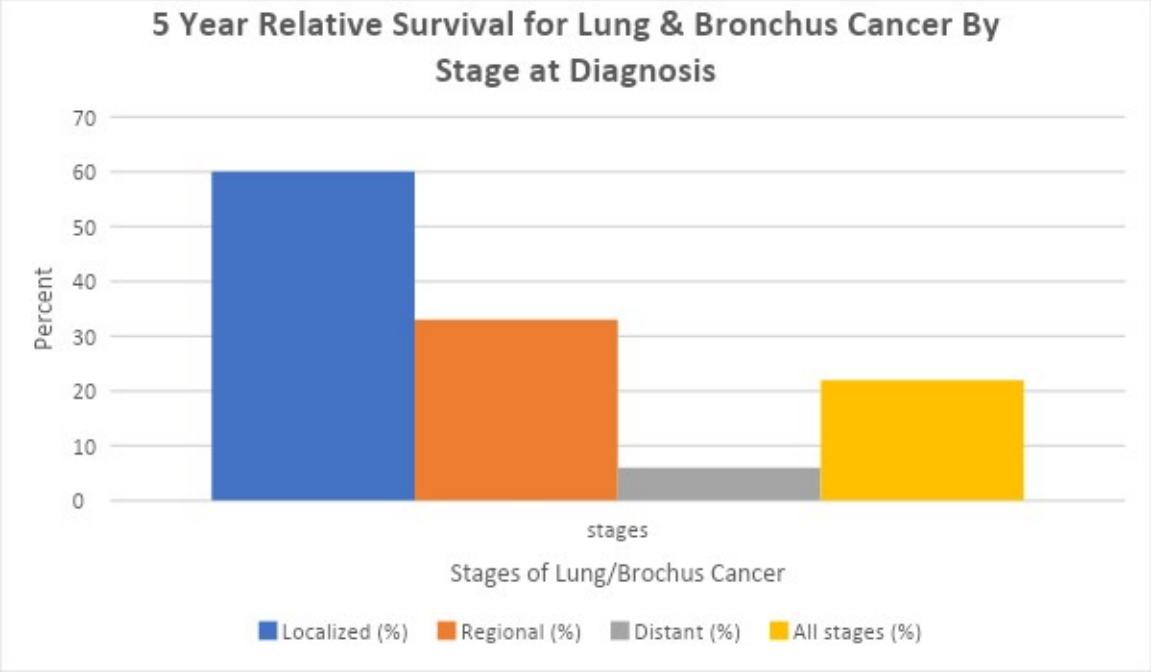


Very simply put – early detection of lung cancer translates into higher survival rates. Lung cancer screening among high-risk populations (based on age and smoking status) is a critical tool to detect lung cancer early. On average there is a 6.3% chance of an individual developing lung cancer in their lifetime.It has also been established that 16 million plus life years have been saved in the U.S from early detection screenings (TruDiagnostic.com). The 5-year survival rate for early-stage lung cancer is greater than that for advanced stage lung cancer. The average 5-year survival rate for all lung cancer patients is 18.6% because only 16% are diagnosed at an early stage. Those patients diagnosed early with a CT scan have a 20-year survival rate of 80%. Patients with Stage 1A lung cancer have a 5-year survival rate exceeding 75% (Li, 2022). The 5-year survival rates for SCLC include: 30% (localized), 18% ((Regional), and 3% (distant) (cancer.org, 2024). The 5-year survival rate for NSCLC includes: 65% (localized), 37% (regional), and 9% (distant) (cancer.org, 2024). This purports the strong utility and value of EPISEEK screenings. As stages increases, the long-term survival rate dramatically decreases. For example, the average 5-year survival rate for Stage IV lung cancer is less than 10%.

LDCT screenings decrease lung cancer mortality by 10.8% (23.5 thousand deaths); 10.3 life years are gained per lung cancer death prevented. Overall, LDCT scanning decreased mortality by 26% in high-risk men and 61% in high-risk women over a 10-year period (De Koning, 2018). Ultimately, LDCT scans reduce lung cancer deaths by 20%. EPISEEK screenings reveal the potential they have to decrease mortality rates, however it is unknown specifically by how much due to lack of prospective and longitudinal studies that have been published on this topic and in this domain.

Since USPSTF recommendations, up to 417 million people were eligible for cancer screenings. Assuming perfect adherence to screening recommendations, the life years gained

from lung cancer screenings are estimated to be 0.5 million (Philipson, 2023). Furthermore, combined screening has saved 12.2-16.2 million life years since the inception of USPSTF recommendations. Therefore, single site screenings like EPISEEK, could have saved an additional 3.2-5.1 million life years. It is also significant to note that 320 screens have to be performed to save a life pertaining to lung cancer per Dr. Bixby, an interventional pulmonologist. (Bixby, 2024).



This data is from 2011-2017.

The development of screening diagnostics for oncology is extremely challenging largely because of the sheer complexity of cancer. The focus is challenging due to the complex biology of cancer and the multifacetedness/heterogeneity of the tumor microenvironment (histological subtypes & endotypes). Oncological biomarkers that are often exploited include: germ like variants like BRCA1 and BRCA2, genomic instability, somatic gene mutations, differential gene expression signatures, tumor suppressor genes, tumor mutation burden, microsatellite instability, epigenetic variants, methylation status, proteins (HER2), miRNAs, EVs such as

exosomes, and post-translational modifications. Also, the proteins in DNA Mismatch Repair (MLH1, MSH2, MSH, and PMS2) can serve as biomarkers.

Additional challenges in EPISEEK screening include: overcoming, navigating, and mitigating the risks that may be posed. Risk is contestable and culturally determined (Donovan, n.d). These risks include: safety, analytical validity (sensitivity, specificity, reproducibility), false positives, false negatives, clinical validity predictive value of a test for a clinical status), clinical utility (importance of result for case), and public health impact. EPISEEK does not detect all cancer types and it does not identify the tumor site of origin. This screening test is designed to rule in a disease state and to minimize false positive results in healthy individuals. This test may not perform well in patients with a personal history of cancer or with symptoms or clinical findings that make cancer more likely (TruDiagnostic, 2024). EPISEEK does utilize an algorithm that was created to minimize false positives, however, it is implausible to circumvent all of these. There is limited sensitivity in detecting early-stage cancers as there is not enough abnormal DNA circulating in the blood to be detected. Optimizing the sensitivity comes at a profound risk of decreasing the specificity since the two are inversely related.

False positive results are most likely to occur when the disease prevalence/incidence is low. Causes of false positive results include: cross-reactivity, batch effects, inefficient probe design, instrument failure, cross-contamination, and tumor heterogeneity. Also, false positive results can be attributed to DNA shed from normal cells, individual germline variants or noncancerous somatic variants such as clonal hematopoiesis.

Adverse effects of false positives include: unnecessary surgical interventions and radiation exposure and biopsies (infections, pain, and bleeding), consumption of unneeded medications, and psychological impact on the patient and the patient’s family.

False negative results are most likely to occur when the disease prevalence/incidence is high. They can be due to low amounts of tumor DNA shed below the assay’s technical limit of detection.

Adverse effects of false negatives in EPISEEK would cause a sense of false security in an individual, as well as, the potential of the cancer to advance/progress to later stages, whereby it would be more difficult to treat later.

Another challenge in EPISEEK is tight control of pre-analytic variables such as avoiding blood cell lysis which increases dilution of tumor circulating fragments from genomic DNA. This challenge is minimized utilizing special collection tubes that stabilize cfDNA by inclusion of additives and preservatives. Also, another pitfall of platforms like EPISEEK is that a high amount of cfDNA can be attributed to other conditions like lupus and inflammatory conditions, not necessarily cancer-driven. So, it is important to discern the two.

In addition, challenges in obtaining reimbursement exist including: affirmative coverage, appropriate coding, and value-based payment for novel diagnostics as EPISEEK. Evidence purports that novel assays like EPISEEK cannot thrive without reimbursement. Reimbursement coverage and payment is the culmination of a diagnostic's value proposition, transcending other levels of validation (Gustavsen, 2010).

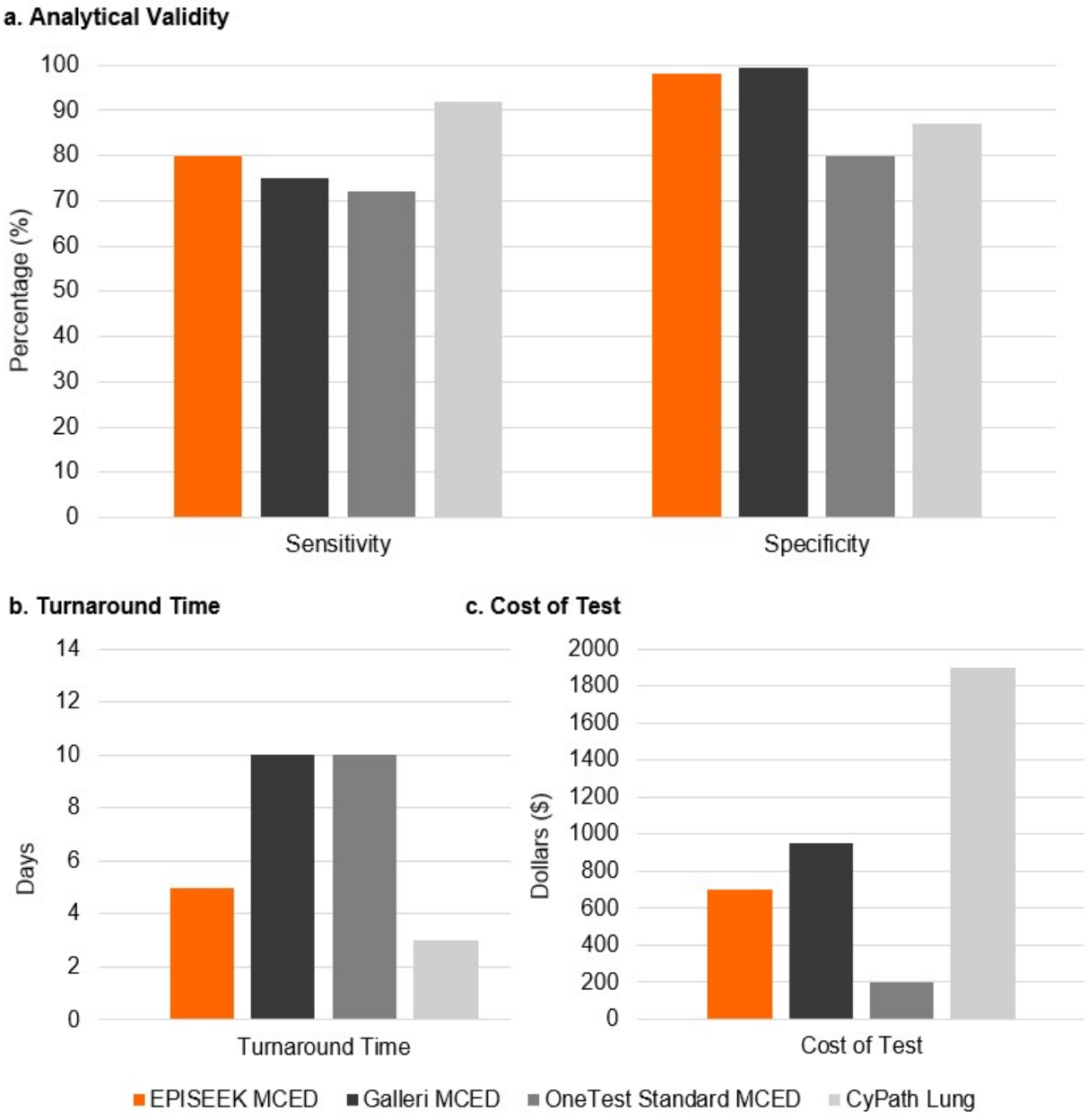
LBs analyze cfDNA, whereas standard biopsies analyze genomic DNA. The collection procedure of liquid biopsies is simplistic, not time-consuming and minimally invasive via a blood sample, whereas standard biopsy procedures are invasive, time-consuming (hospitalization may be required), and tissue intensive. Liquid biopsies reveal a comprehensive tissue profile, whereas standard biopsies unveil only a localized sampling of tissue. With liquid biopsies one could undergo repeated sampling throughout treatment versus standard biopsies an individual cannot due to high risk and pain thresholds. In addition, with liquid biopsies there are no histological evaluations that need to be performed subsequent to the test as in standard biopsies which require a trained histologist or pathologist to examine and result in the specimen. Finally, in other technologies the assay detects tumor of origin sites in which positive predictive

values (PPV) are less than 50%, whereas, EPISEEK does not look for tumor of origin sites and does not have to incur PPV challenges.

EPISEEK, compared to a known platform – GRAILS Galleri, holds great precedence in the market. EPISEEK has a shorter turnaround time of 5 days versus 10 days for GRAILS galleri. Also, EPISEEK uses qPCR while GRAILS Galleri uses NGS. Most importantly, the sensitivity for lung screening is 80% and specificity is >98% versus Galleri's sensitivity of 75% and specificity of >99%.

It is significant to examine both the analytical and clinical validity of EPISEEK given its reliance on proprietary biomarkers and methylation status. Based on comparative data analysis EPISEEK surpasses and outperforms ⅔ competitors in sensitivity, specificity, turnaround times, and cost effectiveness. Furthermore, EPISEEK exhibits fewer false positive and fewer false negative rates than ⅔ competitors, whereby outperforming them in this sector, again highlighting the robust clinical validity of EPISEEK. It can be further elucidated and emphasized that based on its scientific validity EPISEEK is unequivocally both exquisite and a top competitor in today's market.

Figure 12 – Market Comparison of New Cancer Screening Liquid Biopsies



Disadvantages of other screening platforms like low dose CT scans include: the heterogeneity of tumor samples is a limiting factor for invasive methods and it is difficult to obtain a holistic image of the tumor as multiple invasive biopsies may have to be performed to accomplish this (Lone, 2022). Also, LDCT has a high false positive rate - > 96%, indicating the

presence of cancer when it is not there. In a 2017 study 59.7% of patients screened using LDCT had a positive result, with 97.5% being false positives (Kinsinger, 2017). This further highlights the need for novel and accurate screening methods like EPISEEK to pave the way for the future in lung cancer diagnostics.

EPISEEK can improve screening compliance in high-risk groups by its sheer accessibility (doctor's office), non-invasiveness, simplistic and convenient blood test, scalability, more inherent trust in qPCR by individuals, and offering an affordable price point.

Recent research from the University of Chicago purports that 14% of cancers in the U.S are diagnosed subsequent to the patient having a recommended screening. Also, a staggering 16 million plus life years have been saved in the U.S from early detection screenings. To date, an astounding 57% of cancer diagnoses do not have a recommended screening test, these accounting for 70% of all cancer related deaths. This further highlights the value and utility of EPISEEK as a technological platform of great acuity and strength.

COST ANALYSIS

Economic Burden of Lung Cancer

It is important to describe the financial costs associated with the screening, diagnosis and treatment of lung cancer upon the payor, whether that be the patient, or healthcare establishments in the United States. This helps provide a baseline as to the various costs of screening, follow-up tests, diagnostic tests, treatment, and management for the disease. There have been relatively few studies aimed at quantifying the medical costs to patients with lung cancer. Despite being the third most frequently diagnosed cancer, advancements in early detection have been limited. Less than a third of non-small cell lung cancer (NSCLC) patients are diagnosed at stages I/II which are

pivotal for optimal treatment outcomes due to the localized nature of the disease (Apple et al., 2023).

Patients diagnosed with cancer may face significant out-of-pocket (OOP) costs. However, lower costs may be achieved if it can be identified, diagnosed, and treated at earlier stages before the tumor can metastasize. A study was recently conducted that compares costs by cancer staging at diagnosis in commercially insured patients in the United States. These OOP costs included copay, co-insurance, and deductibles (McGarvey et al., 2023). This 2023 study found that the OOP cost per person for lung cancer increased at later stages of diagnosis (stages III and IV) over three years, reaching the highest cost of all cancers observed at $35,243 (per year) (McGarvey et al., 2023). The OOP costs per year of lung cancer consistently increase regardless of staging.

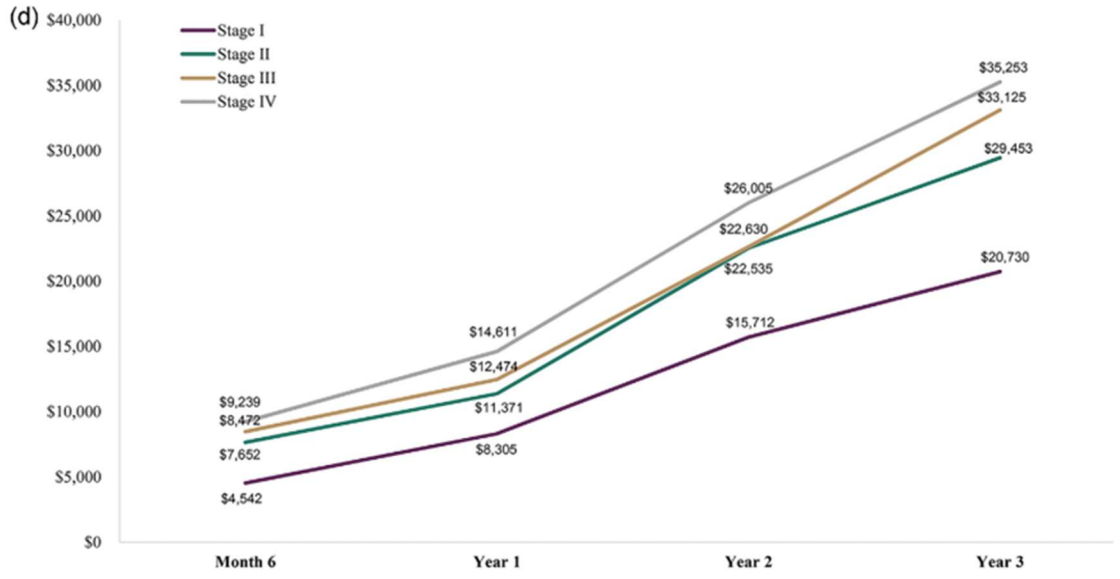


Figure 13. Cumulative out-of-pocket cost by stage at diagnosis for lung cancer (McGarvey et al., 2023).

To further assess the downstream costs associated with lung cancer and its associated healthcare and economic burden on the US population, healthcare resource utilization and related

medical costs were assessed. These parameters include disease staging, receipt of adjuvant and neoadjuvant chemotherapy, phase of care, and surgery type (Apple et al., 2023). HRU was described as the number of events per 1000 persons per month and medical costs were reported in 2021 US dollars per person per month (PPPM) (Apple et al., 2023).

Surgical resection is the most common downstream treatment and an essential component of standard of care for resectable NSCLC. Nevertheless, a significant number of patients encounter systemic post-surgical recurrence, which typically has poor prognosis value with the risk of recurrence increasing with the primary cancer stage (Apple et al., 2023). Treatment guidelines therefore recommend adjuvant therapy to reduce this risk of recurrence. It is questionable whether this creates further economic burden to the patient, but it is certain there is an invasive health burden chemotherapy takes on the mind and body. In one study from the National Cancer Database of 12,473 NSCLC patients of varying stages (I-III) receiving adjuvant chemotherapy to eliminate residual disease post-resection, it was shown that there was reduced mortality risk compared to resection alone (Apple et al., 2023).

Patients with stages 1B-IIIA NSCLC who underwent surgical resection of the primary tumor were identified from the SEER–Medicare database between July 1st, 2011 and December 21st, 2017 (Apple et al., 2023). It is noteworthy that compared to patients who underwent surgery alone, those who received adjuvant treatment experienced reduced rates of NSCLC-related hospitalizations but higher rates of NSCLC-related visits to the emergency room and outpatient clinics (Apple et al., 2023). Additionally, patients in the adjuvant therapy group incurred lower average NSCLC-related medical costs, primarily due to reduced hospitalization expenses (Apple et al., 2023). Overall, patients with later disease stages at diagnosis tended to have numerically higher rates of NSCLC-related hospitalization. These findings suggest the importance of early screening methods for financial liberation, not to mention the mortal benefits.

Healthcare System Impact of Lung Cancer

The recent (2021) expansion of lung cancer screening guidelines set for by the USPSTF is projected to more than double the number of eligible Americans that qualify for lung cancer screening (Copeland et al., 2023). Currently, approximately two million Americans are diagnosed with a new pulmonary nodule annually, with an estimated 80,000 requiring surgical evaluation due to suspected malignancy (Copeland et al., 2023). Meeting the challenge of delivering high-quality, equitable, and affordable lung cancer care to high-risk populations will be compounded by the growing demand for limited oncology services and the substantial costs associated with providing specialized and resource-intensive treatments (Copeland et al., 2023)

US Private and Commercial Insurance (Pre-Medicare)

Lung cancer screening is a covered service under the 2010 Patient Protection and Affordable Care Act (PPACA), which requires non grandfathered private and commercial insurers to cover US Preventative Service Task Force (USPSTF) Grade A and B recommendations without cost sharing (ie, without deductible or copayment). Annual screening with LDCT is covered under Medicare as a preventive health benefit for beneficiaries meeting eligibility criteria, and most state Medicaid programs also cover lung cancer screening. Evidence supports the cost-effectiveness of LDCT, with incremental cost-effectiveness ratios (ICER) below the generally accepted willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY) (Tailor et al., 2022).

Relative to the Lung Computed Tomography Screening Reporting and Data System (Lung-RADS), Toumazis et al.states that a hypothetical diagnostic biomarker lung cancer screening program following the USPSTF guidelines in addition to LDCT-CAD assisted imaging would be cost-effective; if, the screening has at least 90% specificity and a medium sensitivity profile that costs $250 or less (2021). If the same biomarker diagnostic cost $500 or less with a

high sensitivity profile, it would also be considered cost-effective (Toumazis et al., 2021). When the cost eclipsed $750 it no longer was cost effective using the willingness-to-pay threshold of $100,000 per QALY (Toumazis et al., 2021).

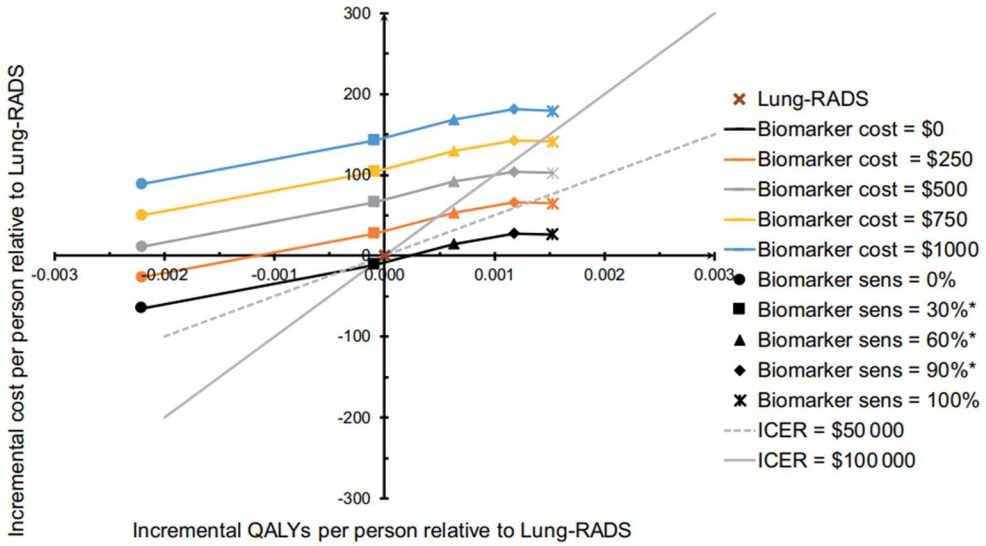


Figure 14. Cost-effectiveness of a hypothetical liquid biopsy with a diagnostic biomarker following the 2013 USPSTF recommendations on lung cancer screening with varying sensitivity and cost, at a fixed specificity of 90% versus the current USPSTF recommendations on lung cancer screening with Lung-RADS followup (Toumazis et al., 2021).

Lack of health insurance and inadequate access to care could contribute to gaps in screening. Lung cancer screening rates are 3 times higher among the insured than the uninsured (Sun et al., 2021). The costs of screening are high, and health insurance reduces the cost to patients.

Downstream Stratification and Analysis

The downstream consequences for lung cancer screening including invasive procedures, costs, and adverse outcomes are still not well understood.

To better evaluate the rate and type of downstream invasive procedures after LDCT examination, one study was conducted evaluating an employer-insured population. A total of 6,268 patients received at least one low-dose chest CT; 462 received at least one procedure within 12 months after screening (needle biopsy 69.0%, cytology 23.6%, bronchoscopy 18.6%, surgery 23.8%). Women and patients ≥65 years were more likely to receive a downstream procedure. Ninety-three patients were diagnosed with lung cancer after screening. The total cost of managing this population of lung screeners was $5,060,511.04, with an average per-episode total cost of $740.06 (Tailor et al., 2022). The aggregate OOP costs to this population of lung screeners was $427,069.74, with an average per-episode OOP cost of $62.46 (Tailor et al., 2022).

To better evaluate the diagnostic costs leading up to a lung cancer diagnosis in patients with abnormal computed tomography (CT) scans, a retrospective cohort study using 5% Medicare claims data was conducted from January 1, 2009, to December 31, 2011. Out of 8,979 patients identified with an abnormal chest CT scan, 13.9% were diagnosed with lung cancer within 12 months. Chest x-rays were the most frequently used diagnostic test. Among the 19% of patients who underwent a biopsy, 43.6% were not diagnosed with lung cancer during the follow-up period (Lokhandwala et al., 2017). The average total diagnostic assessment cost per patient was higher for those diagnosed with lung cancer compared to those who were not ($7,567 vs. $3,558). For patients not diagnosed with lung cancer, the median diagnostic cost per patient was approximately 28 times higher for those who underwent a biopsy compared to those who did not. The total cost for lung cancer diagnostics in the study sample was $38.3 million, with 43.1% of this amount attributed to patients who underwent biopsies but were not diagnosed with lung cancer; this figure also includes adverse events as a significant contributor to increased costs (Lokhandwala et al., 2017). Improved risk stratification is therefore necessary to reduce unnecessary biopsy referrals and associated costs (Lokhandwala et al., 2017). Such strategies may also serve to curb lung cancer malpractice lawsuits, many of which are filed for delayed diagnosis (Miller and Zois, 2023). Between 2006-2015, lung cancer represented the highest

number of medical malpractice cases filed for all cancers, with a total payout of nearly $105 million dollars (Newman-Toker et al., 2019).

The mortality benefits of lung cancer screening are well documented, however the downstream consequences are not yet well understood. In this review we aim to propose a staging lung cancer workup for high-risk individuals. It is common for symptomatic patients to receive LDCT. Liquid biopsy can be an alternative or complement screening process. From here, a decision tree model can be used to decide whether the patient is in need of a tissue biopsy or confirmation via LDCT/Liquid biopsy. This proposal aims to reduce the amount of unnecessary invasive procedures to the patient.

Cost Analysis of EPISEEK vs. LDCT vs. No-Screen

Our cost analysis operates on the premise that regular screening results in cost savings and mortality benefit over time: screening allows for detection of cancer in its earlier stages, ideally avoiding the higher costs and lower survival rates of treating later stages of cancer (Harpaz et al., 2023). In 2021 the USPSTF updated their previous screening guidelines, recommending annual LDCT screening for high-risk individuals who are now defined as: current or former smokers (having quit within the last 15 years) aged 50 to 74, with a smoking history of at least 20 pack-years. These guidelines were based on maximizing the benefits while minimizing the harms of screening (e.g. low-dose radiation, incidental findings) without regard to cost. While other studies have put forth more economical screening strategies, these guidelines have overall been found to be cost-effective (Criss et al., 2019).

To perform a cost analysis on EPISEEK vs. LDCT vs. no screen, we considered the following factors: upfront and processing costs of each test, health utility values, and qualitative assessments of each screening method. Our results are summarized in Table LC1. The

EPISEEK test currently lists for $699, compared to Grail's Galleri at $949; comparisons to other tests are illustrated in Figure LR1 (Precision Epigenomics; Galleri). Prior to the passage of the Affordable Care Act, LDCTs cost on average $1130; however, the scan is largely covered for high-risk individuals between the ages of 50-77 (Black et al., 2014). Out-of-pocket, LDCTs now typically range from $300-500 (Cressman et al., 2017).

Tentatively, the EPISEEK test has similar sensitivity, specificity, and timeline of detection to LDCTs; pending further data our analysis therefore assumes comparable health utility values for the purpose of calculating quality adjusted life years (QALY) and incremental cost-effectiveness ratios (ICERs). Importantly, novel diagnostic tests may report higher sensitivities in preliminary trials due to elevated rates of cancer diagnoses in validation cohorts. As tests similar to EPISEEK (e.g. Grail's Galleri) have progressed to larger trials, reported sensitivity levels have slightly decreased as trial cohorts have increased (Zhu et al., 2023).

Because implementation and processing of LDCTs tend to be highly variable, ICERs of LDCTs have previously been shown to range between $11,000 to $207,000 per QALY (Harpaz et al., 2023; Criss et al., 2019). We reviewed one cost analysis of the National Lung Screening Trial (NLST) and two models simulated from NLST data to compare costs associated with LDCT vs. no screen; this data is summarized in Table LC2. These studies were completed prior to the USPSTF's adjusted guidelines and therefore define their high-risk smoking threshold at 30

screening method	direct out-of-pocket cost	LYs gained	ICER per QALY	qualitative benefits
no screen	$0	n/a	n/a	- *No risk of false positives* - *No incidental radiation* - *Convenient in pre-symptomatic stages*
LDCT	$300-500	0.0316	$49,200-$81,000	- *Covered for high-risk individuals by most insurers* - *Established method recommended by USPSTF and CMS*
EPISEEK	$699	0.0316†	$49,200-$81,000†	- *Available directly to consumers* - *Lower productivity and administrative cost burden: blood draws are more convenient for both patient and provider than CT scans* - *Reduced personnel cost: does not require interpretation by radiologist* - *Competitively-priced MCED: screens for multiple solid tumors, including lung, breast, prostate, and colorectal cancers, in addition to cancers that do not currently have any recommended screens (e.g. pancreatic)* - *Avoids false positives in patients with fungal cocci (Valley Fever)*

Table LC1: A summary comparison of three screening methods based on available data. ICERs were based on a willingness-to-pay threshold of $100,000/QALY. †Pending further data, health utility values for EPISEEK are presumed to be similar to those for LDCT; values here reflect ranges determined by previous studies (Black *et al.*, 2014; Criss *et al.*, 2019).

(compared to 20) pack-years, and lower age threshold at 55 (compared to 50). Black et al. analyzed NLST data using mean life-years (LYs); QALYs as determined by quality-of-life surveys completed by patient subgroups; costs per person, including utilization rates and Medicare reimbursements; and ICERs using a $100,000 per QALY willingness-to-pay threshold. They found that LDCTs cost $1631 more per person over their lifetime compared to no screening, with 0.0316 and 0.0201 LY and QALY gain per person, respectively (Black et al., 2014).

Using NLST data, Criss et al. published a model comparing populations of current and former smokers screened based on NLST enrollment criteria (ages 55-74), USPSTF guidelines (ages 55-80), and CMS guidelines (55-77). Total costs across the simulated population for no-screen was $295 million, with incremental increases for the NLST, USPSTF, and CMS guidelines being $87, 98, and 93 million, respectively; no differences in mean LY nor QALY were determined. USPSTF guidelines proved to be the least cost-effective, at $96,700 ICER per QALY compared to $49,200 and $68,600 for NLST and CMS guidelines, respectively (Criss et al., 2019).

Cressmen et al. developed their model using both NLST and Pan Canadian Study data, to compare costs of LDCT vs. no screen in a high-risk subgroup to evaluate a Canadian screening program. Interestingly, while they estimated the societal cost of implementing such a program to be CA$668 per person, this study found reduced cost efficacy of a national lung cancer screening program due to lower drug and treatment prices relative to the US; the greatest factors of cost-effectiveness in their study were screening mortality rates and long-term improvements in quality of life. Compared to no-screen, screening with LDCT in this study yielded QALY gain of 0.032 and CA$20,724 ICER per QALY (Cressmen et al., 2017).

Cost Analysis Using Models

Given the length of time liquid biopsies have been available on the market, our literature search returned no real-world studies comparing the cost-efficacy of liquid biopsy tests to Standard of Care/Usual Care screening options, either as replacements or complements. However, many predictive models have simulated such comparisons, and in most models liquid biopsies were predicted to be cost-effective as screening tools compared to Standard of Care (SoC) methods across multiple cancer types: colorectal, gastric, breast, and brain (Fagery et al., 2023). Deibel et al. compared numerous biomarker assays (including a methylated DNA-based liquid biopsy: Epi proColon; Epigenomics Inc., Berlin, Germany) to colonoscopy and no-screen in a single-disease model, and found that all non-no screen methods were cost-effective, with the biomarker assays scoring significantly higher rates for annual screening compliance compared to colonoscopy (Deibel et al., 2021). Conversely, one study directly compared the cost of liquid biopsy to colonoscopies; using the current market price of Grail's Galleri MCED, colonoscopy was found to be more cost-effective than the new liquid biopsy screening option (Aziz et al., 2023).

Tafazzoli et al., established a model to predict the value based price of an MCED test that screens for 19 solid tumors, including lung cancer. The MCED is intended for use alongside SoC screening, and accounting for additional screening costs from misdiagnoses and false positive workups, costs an incremental average of $12,919 more than SoC alone. At a threshold of $100,000/QALY, the authors estimated a value-based price (VBP) of $1196 (alternatively, VBPs of $767 at $50,000/QALY, and $1625 at $150,000/QALY). Importantly, the authors were able to demonstrate that adding the MCED test to SoC screens resulted in earlier diagnoses, subsequently leading to increased survival and reduced treatment costs overall; for lung cancer alone, ICER per QALY was projected to be $60,282 (Tafazzoli et al., 2022). Lipscomb et al., put forth another model–using disease prototypes roughly based on pancreatic, uterine, and lung

study	database	population	screening methods	total cost	cancer screened	cancer cases	cancer deaths	mean life years	QALYs	ICER (per QALY)	ICER (per LY)
Black *et al.*, 2014 study	NLST (patients followed from 2002-2004 through 2009)	high-risk patients (55-74 years; 30 pack-years) 26,642 in CT group, 26,660 in radiography group	LDCT	$3,074.00		1076	469	14.7386	10.9692	$81,000.00	$52,000.00
			no screen	$1,443.00		978	552	14.7071	10.9491		n/a
Criss *et al.*, 2019 model	based on NLST data	n/a	NLST criteria (screen up to age 74)	$382 million	941	5410	3900	2.8mil	2.3mil	$49,200.00	$36,400.00
			USPSTF recommendations (screen up to age 80)	$393 million	1250	5450	3800	2.8mil	2.3mil	$96,700.00	$51,900.00
			CMS recommendations (screen up to age 77)	$388 million	1110	5430	3840	2.8mil	2.3mil	$68,600.00	$42,600.00
			no screen	$295 million	n/a	5370	4230	2.8mil	2.3mil	n/a	n/a
Cressman *et al.*, 2017 model	based on NLST and Pan-Canadian Study data	high-risk subgroup (n=12325)	LDCT	$668.00					0.032	$20,724.00	
			no screen	$0.00					n/a	n/a	

Table LC2: Comparison of health utility values of LDCT vs. no screen from one retrospective study and two models. LDCT yields 0.0316 additional LYs compared to no screening at an additional cost of $1,631 per person (Black *et al.*, 2014). Model data indicates that CMS guidelines are the most cost-effective compared to USPSTF guidelines and NLST enrollment criteria.

cancers–to predict an MCED's effects on QALYs and medical care costs, specifically in comparison to no screening. This model also incorporates parameters to determine ideal screening intervals, simulated here in a cohort aged 50-70 years tested every two years. Evaluating ICERs for the lung cancer-based prototype alone determined the cost to be $178,813 per QALY, while the multi-cancer model yielded $22,494 ICER per QALY, illustrating the substantial cost-effectiveness of favoring a multi-organ approach over single-cancer screens (Lipscomb et al., 2022). Upon collecting more data assessing EPISEEK's ability to detect lung cancer early along with its sensitivity and specificity (with respect to LDCT), the two models described here should prove invaluable to establishing both a value based price point, as well as a screening regimen that balances clinical and cost efficacy.

Qualitative Cost Analysis

While there is insufficient data to quantitatively distinguish EPISEEK from current LDCT screening methods, it is important to emphasize EPISEEK's qualitative advantages over LDCT, and how these may translate indirectly to cost reductions over a patient's treatment timeline. Procedurally, LDCTs involve a comparatively lengthier CT scan whereas EPISEEK requires a simple blood draw; this potentially confers a significant convenience and time benefit to patients. LDCT scans must be read by a radiologist (or even two), and historically have had high variability in their sensitivities and specificities (Harpaz et al., 2022). EPISEEK is expected to interpret results more consistently, and its qPCR-based platform allows a competitive price-point compared to other emerging liquid biopsies (many of which are NGS-based) (Zhu et al., 2023; PE citation?). As an MCED, EPISEEK also contributes to the shifting of cancer diagnostics towards a universal cancer screening paradigm. MCEDs have the potential to be more efficient than single-site screening, detect cancers too rare to be regularly screened for, and have a profound impact on mortality reduction across a range of tumors (Ahlquist, 2018; Hubbell et al., 2020). One model based on SEER data predicted that addition of MCEDs to SoC screening reduced mortality 26% across all cancers and tumor growth rates tested (Hubbell et al., 2020).

EPISEEK's convenience and efficiency benefits may also positively impact one of lung cancer screening's chief concerns: poor compliance. While numerous large studies have shown that LDCT screening results in an overall 20% lung cancer mortality reduction, lung cancer particularly suffers from low adherence rates (Black et al., 2014; Midthun, 2016; Criss et al., 2018; Zhu et al., 2023). Lung cancer screening compliance rates are among the lowest of all cancers, with a reported range of 35-50%. A 2021 multi-site study of 668 current and former smokers found that 47% of patients returned for follow-up recommendations, with adherence greater in patients with more concerning baseline findings and in former smokers (Triplette et al., 2021). Across the population, lung cancer screening compliance is lowest in current

smokers, minority populations, and individuals of lower socioeconomic status (SES), suggesting a need for more education and outreach (Lopez-Olivo et al., 2020; Kunitomo et al., 2020). Pilot studies assessing the impact of employers offering MCEDs as a benefit have identified this as a potential pathway to expand screening access to low SES individuals, especially when encouraged in-person by those who speak the same language (Jamal et al., 2023).

Larger study centers tend to report relatively higher rates of compliance, possibly due to a more robust care infrastructure (Triplette et al., 2021). A 2017 study assessing the implementation of a screening program in the Veterans Health Administration surveyed 4246 current and former smokers considered high-risk for lung cancer. 2106 total (49.6%) followed through with LDCT screening; of those, 1257 (59.7%) screened positive for nodules. 73 of these cases were suspected of lung cancer and recommended for biopsies; however only 31 were confirmed positive for lung cancer (20 cases in Stage I) (Kinsinger et al., 2017). This study emphasizes the variability of LDCT processes and patient experiences, underscoring a need for more guidance on diagnosing very small nodules and a remedy for unacceptably high false positive rates. False positive rates for LDCTs have been cited as top reasons high-risk individuals do not comply with screening; future screening compliance has been shown to decrease >50% following a false positive result, especially in smokers (Edward Stefanek, 2011; Ford et al., 2003). Based on currently available data, EPISEEK's specificity does not significantly differ from LDCTs *on average*; however its potential to increase screening compliance in high-risk populations lies in the increased certainty of its false positive rates compared to those of LDCTs. In addition to poor standardization of methods for evaluating nodules radiographically, visual methods for lung cancer screening are further complicated by incidences of parasitic or fungal infections presenting as pulmonary nodules (e.g. the heartworm *Dirofilaria immitis*, or fungi *Histoplasma capsulatum* or *coccidioidomycosis*) (Allison et al., 2004). In this regard, EPISEEK's modality may be of specific benefit to regions where such infections are prevalent or endemic, as in the case of valley fever (*coccidioidomycosis*) in the

southwestern US; even asymptomatic cocci infections may present as nodules on CT scans or x-rays (Peterson et al., 2023; Bixby, 2024). Either as a screening replacement or complement, EPISEEK can potentially eliminate unnecessary testing arising from these scenarios.

Perceived low value, practical barriers, and patient unawareness have also been commonly cited as reasons for screening noncompliance (Carter-Harris et al., 2017; Bixby, 2024); therefore, in addition to increasing education for both providers and patients alike, EPISEEK MCED's qualitative advantages can address unmet patient needs and ultimately increase screening compliance. In the current market, high-risk patients who are not yet eligible for free LDCT screening stand to benefit the most from a low-cost MCED such as EPISEEK (Zhu et al., 2023).

Substantially increasing screening compliance could save billions of dollars when accounting for both monetary and indirect (e.g. quality of life, productivity, caregiver burden, etc.) costs (Philipson et al., 2023). In a micro-model, Criss et al. simulated lung cancer mortality reductions across a range (25-100%) of compliance rates; improving adherence from 45 to 65% resulted in an incremental mortality reduction of 1.56%, representing an additional 27,745 deaths avoided between 2016-2030 (2018).

Further Considerations for Cost Analysis

From a precision medicine perspective, future economic impact studies should consider the multitude of individual factors that determine a test's cost efficacy for any given patient, including unique treatment timelines, and patient characteristics and histories. To this end, this study recommends a cost-effective screening regimen that modifies current screening guidelines, and offers the EPISEEK test as both a standalone screen for otherwise noncompliant high-risk individuals, and as a complement to LDCT. Several studies have proposed adjustments to current USPSTF lung cancer screening guidelines to increase cost

efficacy while targeting those at highest risk for lung cancer (Criss et al., 2019). Toumazis et al. posits that incorporating risk thresholds specific to models, such as the $PLCO_{m2012}$ risk prediction model or Lung Cancer Death Risk Assessment Tool, increased QALYs of LDCT screening for less cost compared to following the 2021 USPSTF recommendations (2023). An example screening regimen is illustrated in Figure LC1.

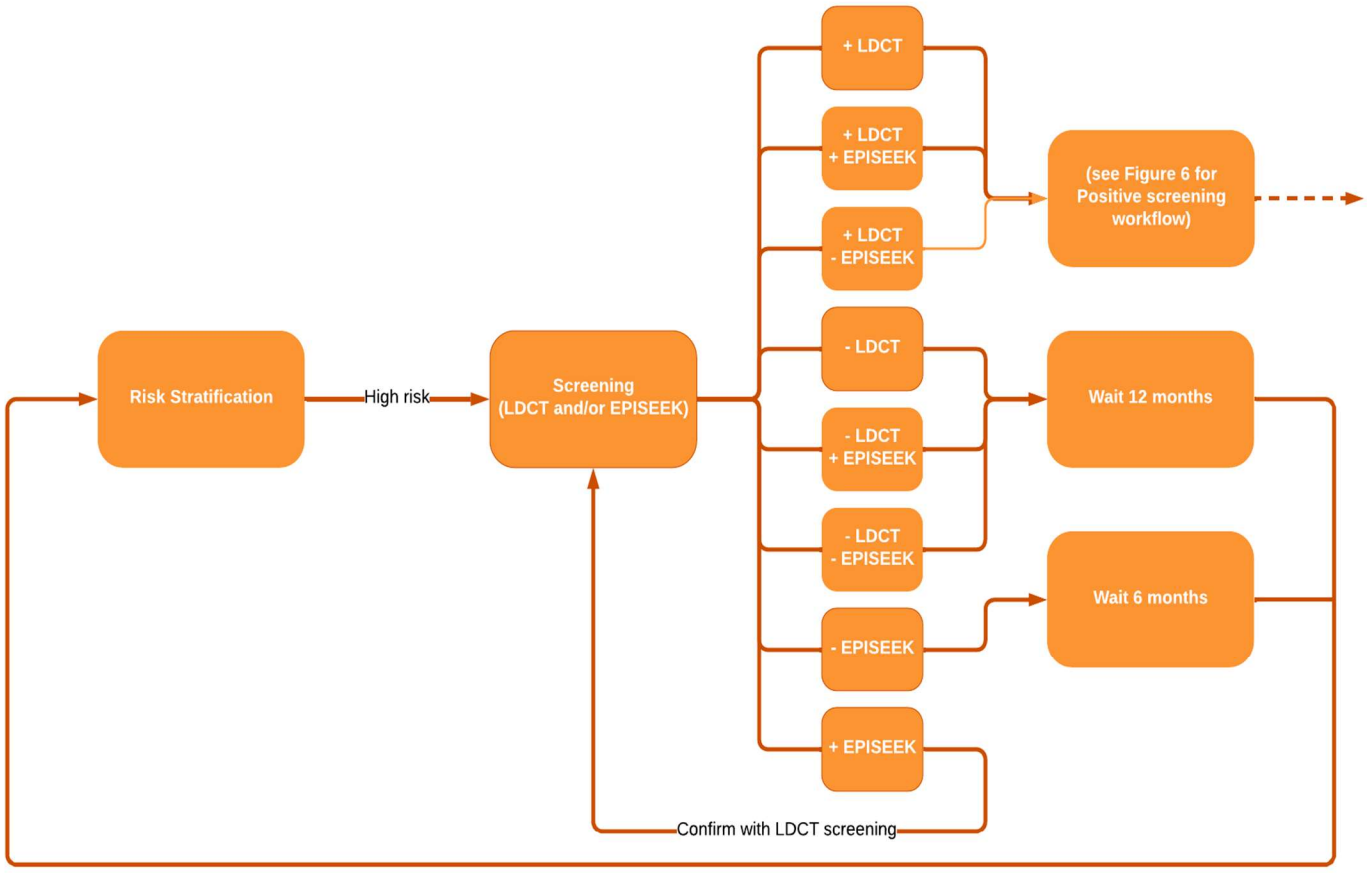


Figure LC1: Prospective screening schematic for incorporating EPISEEK into lung cancer screening regimens. Risk stratification has been shown to be cost-effective when using the 1.2% threshold of the PLCOm2012 model; this effect is not limited to this single model, but Toumazis et al. caution that thresholds are specific to their parent models (2023). Patients deemed at high-risk for lung cancer using vetted models should then be screened using EPISEEK either alone or complementary to LDCT.

Ideal Price Point

Liquid biopsies that use PCR-based technologies promise early detection at a lower cost (Zhu et al., 2023). The aforementioned study by Tafazzoli et al. estimated the value based price of a similar MCED to be $1196, though this MCED allegedly detects cancer earlier than SoC screening alone. EPISEEK does not claim to detect lung cancer significantly earlier than LDCT, and because it screens for fewer total solid tumors than the reference MCED, our market research suggests EPISEEK's current list price of $699 is appropriate, pending more data on its clinical and health utility.

Market Strategy of EPISEEK

Precision Epigenomics strives to develop an effective and affordable solution for early cancer detection. Their mission as a company is to improve how cancer is detected and treated through advanced diagnostic tools (P.E., 2024). EPISEEK is listed at $699, which is less expensive for those that are commercially available around $1000 (Mauracher, 2023). With its business-to-business partnership with Trudiagnostic, P.E. has been able to market its device through subscribed practitioners (Ashford, 2024). Trudiagnostics has also taken up the courtesy of promoting and marketing EPISEEK along with its distribution and sales (Ashford, 2024). The GRAILS Galleri test is a similar MCED test uses LB with NGS. The GRAILS Galleri test is listed at $949 per testing kit and can also be purchased through Trudiagnostic (Galleri, 2024). Although clinicians can purchase the GRAILS Galleri test on Trudiagnostic, some may choose EPISEEK, which is much more targeted, specific and is less expensive.

Emerging Market Growth of MCED Tests

The utilization of LB in MCED is expected to grow within the near future. The market for LB is expected to increase by 16% from 2020 to 2030 (Connal et al., 2023). MCED tests have created an opportunity to detect and treat cancers earlier at a curable stage where healthcare costs are not as financially damaging to patients. As malignancy advances in patients, the financial burden increases with each staging period. The average a cancer patient spends on treatment costs is $48,300 for stage I-II, $72,600 for stage II-III, and $83,900 for stage IV (Connal et al., 2023). It is critical to recognize the significance of earlier cancer detection and the physical and financial effects a patient may experience. The application of LB in MCED will play a pivotal role in cancer screening and management, reducing the treatment costs for several patients and increasing life expectancy.

Feasibility of MCED Tests

Several opportunities for LB in MCED have already established themselves paving the way for the innovative technology. The NIH has launched its research network, The Cancer Screening Research Network (CSRN), to evaluate emerging technologies in cancer screening. The CSRN plans to launch the Vanguard Study in 2024 which will focus on addressing the feasibility of MCED tests in randomized controlled trials (U.S. Dept. HHS, 2024). The purpose of the study is to determine if MCED tests can detect cancers at an earlier stage reducing deaths and if the benefits of MCED tests outweigh the potential harms (U.S. Dept. HHS, 2024). Data collected from the clinical trial will be the foundation for developing evidence-based screening guidelines (U.S. Dept. HHS, 2024). The CSRN also aims to support the White House Cancer Moonshot goal initiated by the Biden-Harris administration. The Moonshot goal is a national effort to help end cancer as we know it with two main goals; (1.) Prevent more than 4 million

cancer deaths by 2047 and (2.) improve the experience of people who are touched by cancer (U.S. Gov, 2022). The Moonshot goal has already announced 95 new programs including 170 companies, non-profits, and academic institutions starting collaborations in support of the goal (U.S. Gov, 2022). The future for LB in MCED will continue to progress and continuing studies will help address the feasibility in cancer screening.

Anticipated Challenges of MCED Tests

Although LB in MCED appears to have a promising future, several anticipated hurdles and barriers make the technology difficult to use widely, such as their lack of standardization and FDA approval. Due to a lack of standardized protocols, LB often suffers from reproducible results within workflows causing inconsistency. The pre-analytical phase which includes specimen collection, stabilization, transport, enrichment, processing, isolation, and quality assessment of the analyte is a critical process of LB where 46-68% of errors often occur (Crawford-Brown, 2020). The standardization of LB needs improvement and several international organizations such as SPIDIA4P, CANCER-ID, and BloodPAC are working on developing methods for standardization including a data infrastructure to be shared among stakeholders to reach a consensus (Crawford-Brown, 2020).

Regulation of MCED Tests

In addition, there are no MCED tests that are FDA-approved, however; they are regulated under Clinical Laboratory Improvements Amendments (CLIA) as a Laboratory Developed Test (LDT) (DCP, 2024). EPISEEK is an example that follows the regulation under CLIA as an LDT. Consumers may still purchase MCED tests such as EPISEEK with the exception that it is prescribed or ordered by a licensed healthcare professional. MCED tests without FDA approval prevent the assay from receiving full coverage or reimbursement from healthcare insurance companies such as Medicare, Medicaid, or private parties. The Centers

for Medicare and Medicaid Services (CMS) currently do not recommend any MCED tests for reimbursement, therefore; health insurance companies will not pay for them prompting consumers to pay out-of-pocket for the test (DCP, 2024).

FDA Oversight of LDTs

While MCED tests can be offered to market as an LDT, the FDA has proposed its new rule on the oversight of LDTs effective as of April 2024. The FDA has announced that all LDTs such as in-vitro diagnostic (IVD) products and manufacturing laboratories of IVDs are considered to be under the Federal Food, Drug, and Cosmetic Act (CDRH, 2024). The FDA's oversight of LDTs will follow a four year phase-out process in agreement with the enforcement discretion (CDRH, 2024). All tests including those for diagnostics and screening methods will need to follow the rules and regulations provided by the FDA to market their device. The oversight of LDTs is to ensure that all devices are safe and effective to use. Depending on the type of testing device and level of risk, LDTs will be classified into three different classes; Class I (low to moderate risk), Class II (moderate to high risk), and Class III (high risk). Class I devices are exempt from Premarket Notification, Class II requires a Premarket Notification (510k) and Class III requires a Premarket Approval (PMA) (CDRH, 2024).

FDA Approval of MCED Tests

For MCED tests to get FDA approval, clinical evidence needs to be provided to show clinical validation and effectiveness of the assay. This creates an additional challenge for companies developing MCED tests because they will need to conduct clinical studies on their device which are very costly to perform and can take several years to complete. Depending on the type of clinical trial and phase, the average cost for clinical trials across all therapeutic areas for phases; 1, 2, and 3 averages at the cost of $4, 13, and 20 million (Ledesma, 2024). Furthermore, companies performing clinical trials on their MCED tests will also need to follow

the rigorous FDA application process for their device. Since MCED tests such as EPISEEK can detect cancer, the assay falls under the class III device and is therefore subjected to premarket authorization (PMA) due to the level of risk associated with the device. A PMA is the most stringent type of device to get marketing approval from the FDA (CDRH, 2019). FDA approval for MCED tests such as EPISEEK will increase the product's market size and create more coverage opportunities through health insurance companies. “The FDA stamp of approval may facilitate earlier reimbursement by both private payers and CMS,” (Rodriguez, 2024).

FDA and CMS Voluntary Programs for Emerging Technologies

Although there are no MCED tests that are currently FDA-approved, there are some devices that have received FDA approval for a Breakthrough Device Designation and Investigational Device Exemption (IDE). The Breakthrough Device is a voluntary program established by the FDA for medical devices that provide more effective treatment or diagnosis of life-threatening or irreversible debilitating diseases or conditions (CDRH, 2024). The advantages of the Breakthrough Device program offers direct interaction and feedback from FDA experts, provides priority review of the premarket submission, and contains benefits concerning reimbursement with CMS (CDRH, 2024). CMS supports the FDA’s Breakthrough Device program and offers coverage for certain devices approved under the program. CMS has also proposed its Transitional Coverage for Emerging Technologies (TCET) pathway in June 2023 which is a voluntary program to help expedite Medicare coverage of emerging technologies. The advantages of the TCET pathway provides national coverage determination (NCD) and coverage with evidence development (CED) processes to expedite Medicare coverage of certain Breakthrough Devices (Fleisher et al., 2023). The goal of the TCET pathway is to

provide support through coverage for Medicare patients and ensure they are receiving the highest quality of care with new and emerging technologies.

MCED Tests Close to FDA Approval

An example of a test that has received FDA approval for the Breakthrough Device Design program is OverC by Burning Rock. OverC is a LB MCED test that uses NGS and can detect esophageal, liver, lung, ovarian, and pancreatic cancer (Seymour, 2023). FDA approval of the Breakthrough Device program facilitates the development, assessment, and review process to market. GRAIL is another example that has received FDA approval for their GRAILS Galleri test for an IDE study. Similar to the FDA's Breakthrough Device program, an IDE is primarily focused on the study of an emerging technology. An IDE allows devices to be studied to collect safety and effectiveness data in a clinical trial (CDRH, 2022). Data received from the clinical trial for GRAILS Galleri under an IDE will be used in hopes of securing premarket authorization for their device from the FDA. The benefits of an IDE have provided the GRAILS Galleri test to be covered by CMS through its Real-world Evidence to Advance Multi-Cancer Early Detection Health Equity (REACH/Galleri-Medicare Study). CMS has approved Medicare coverage of the FDA-approved IDE REACH/Galleri-Medicare study and will cover the cost of the test and related routine items and services for study participants (Davis & Rowland, 2023). The Galleri-Medicare study is a "first-of-its-kind study" designed to collect real-world evidence on the clinical impact of the MCED test for the Medicare population (Davis & Rowland, 2023). The FDA's Breakthrough Device and IDE program do not guarantee FDA approval to market a device but it provides additional support in the process of premarket authorization including potential access to CMS coverage regarding clinical studies.

PCR-Based Liquid Biopsy

Although MCED tests such as EPISEEK face many challenges in the adoption of technology and regulation, several elements of LB influence the advancement of screening and diagnostic methods in healthcare for lung cancer. One advantage of EPISEEK is that it uses real-time PCR or q-PCR which offers rapid results. Other LB platforms that use NGS can typically have much longer turnaround times. This is partly due to the instrumentation and bioinformatics that are needed to perform the test and interpret results. NGS involves instrument cost, price per run, and price for bioinformatics analysis leading to a longer turnaround time of around 1 week compared to other methods (Alexandrou et al., 2023). PCR methods for LB can be a solution to offer a more rapid and inexpensive approach to testing. PCR-based assays generally have a faster turnaround time and are less expensive (Olson, n.d.). GRAILS Galleri is an example which has a turnaround time of about 10 days compared to EPISEEK which has a turnaround time of 5 days.

Minimal Residual Disease and Treatment Response for Liquid Biopsy

Another advantage of LB is that the test is a non-invasive procedure using peripheral blood to obtain CTCs or cfDNA that can easily be repeatable if needed. LB can become an alternative for patients who may have a chance of very high-risk tissue biopsy procedures. This can mitigate invasive tissue biopsy complications that can lead to bleeding, infections, or pain (Noor et al., 2023). LB can also provide a deeper understanding of tumor characteristics through CTCs and cfDNA including the ability to identify minimal residual disease (MRD) and treatment response (Assi et al., 2023). Detecting MRD in a patient will provide healthcare providers with

information if a patient's cancer has relapsed. In addition, determining how well or not well a patient responds to certain treatments will determine if treatment was effective providing an option for a more personalized therapeutic approach. EPISEEK is an example that has been used for MRD and treatment response. Small studies have been done but further research will be part of their continued studies in the following years.

Future of MCED Tests to Complement Current Lung Cancer Screening Methods

While LDCT remains the recommended screening method for lung cancer, further development of LB could change future screening methods with LB or be used to complement current screening methods. Although the USPSTF recommends lung cancer screening with LDCT, LDCT remains severely underutilized (Zhu et al., 2023). While there is not much data supporting why LDCT is underutilized, the National Health Interview Survey data reported that only 4.4% of people who were eligible for screening underwent chest CT for lung cancer screening in 2015 (Zhu et al., 2023). Suggestions for low compliance can be due to inaccessibility or inconvenience of the assay. LB holds great promise for improving access to screening especially if there are barriers to access to health care and where testing can be in a local phlebotomy lab or at the convenience of one’s home (Zhu et al., 2023). EPISEEK is intended to be used as a complementary tool with current screening imaging modalities for lung cancer. In the consideration of treatment response and MRD, EPISEEK and LDCT could become a new routine screening method used for those who test positive for lung cancer and need to determine treatment guidance or monitor disease recurrence.

DISCUSSION

As the need for lung cancer screening and compliance increases with the prevalence of the disease, several factors need to be considered before a definite solution can be determined. LDCT continues to remain the recommended screening method for lung cancer but compliance remains severely low. Although there is not enough data supporting low compliance for LDCT, our study suggests that low compliance to screening can be due to procedure inconvenience, claustrophobia, fear of false positive or false negative results, coverage concerns by health insurers and lack of knowledge from healthcare providers. The rate of false positives and false negatives are largely variable, raising a concern for lung cancer screening with LDCT. This can be due to diverse radiologist experience, instrumentation quality, and CAD systems implementation with or without DL methods. However, LDCT remains a cost-effective approach to lung cancer screening but in the aspect of tumor heterogeneity, treatment selection, and MRD, LDCT is not an effective approach. LB in this case such as EPISEEK can play a vital role in cancer management and treatment selection for lung cancer. EPISEEK has high specificity and sensitivity rates for lung cancer that can present additional information on tumor characteristics that LDCT cannot provide. EPISEEK can also provide healthcare professionals with a more personalized therapeutic approach in treatment selection and identify MRD to monitor disease recurrence. EPISEEK can also provide an alternative to invasive tissue biopsy procedures that may be high-risk to some patients.

MCED tests such as EPISEEK were found to be cost-effective in terms of earlier detection and treatment selection. PCR-based LB technology in particular was found to be more cost-effective with a shorter turnaround time in comparison to other LB technologies using NGS which was not found to be a cost-effective approach. An important component to recognize is that EPISEEK is less invasive, convenient, repeatable, and rapid and has the potential to increase compliance for lung cancer screening and detect cancer earlier than LDCT. LB can break barriers and access to routine screening potentially increasing adherence to screening guidelines, especially within underserved communities (Febbo et al., 2024).

FDA approval of EPISEEK will play a considerable role in the advancement and adoption of technology partly due to the many clinical studies that will be performed to show clinical validation and effectiveness and permit access to coverage and reimbursement. With the FDA's oversight on LDTs, P.E. will need FDA approval for EPISEEK and is anticipating to start their clinical studies later this year in 2024. The FDA's Breakthrough Device Program and IDE are voluntary programs that can provide support for P.E. 's EPISEEK when seeking premarket approval for their device. Additionally, if EPISEEK is approved for a Breakthrough Device or IDE from the FDA, there is potential that their clinical studies could be covered by CMS through the TCET program.

Continuing studies and projects such as the Vanguard study, White House Cancer Moonshot, and REACH/ Galleri-Medicare study will address the feasibility of MCED tests determining if MCED tests can indeed detect cancer within earlier stages. The clinical data provided from these studies will facilitate FDA approval encouraging that widespread adoption of the technology is achievable within the near future. Real-world evidence will play a significant role in showing health benefits through collected data potentially reducing the costs of clinical trials such as the REACH/ Galleri-Medicare study. Reimbursement and coverage from Medicare, Medicaid, and private parties will be very important for the technology to thrive creating opportunities for the technology to become widely more accessible, especially for those in underserved communities. MCED tests such as EPISEEK are creating a paradigm shift in current lung cancer screening methods that could potentially become a part of SoC procedures following treatment selection in cancer management. Further research on both LDCT with EPISEEK needs to be investigated to show potential health benefits in screening. According to our study's findings, earlier detection of lung cancer is critical for patients' health outcomes and financial aspects. Current screening methods with LB such as EPISEEK can lead to a reduction of healthcare costs, increase life-years-gained, and ultimately save lives.

CONCLUSION

Our cost analysis concludes that LB tests such as EPISEEK is cost effective for high-risk patients for lung cancer especially for those who refuse traditional LDCT screening. The current price range for LDCT out-of-pocket is $300-$500 and for eligible high-risk individuals the cost can be covered by health insurance. EPISEEK is listed appropriately at $699 but is not currently covered through health insurance, however; it is important to note that the test holds several qualitative benefits being a MCED test. Referring back to table LC1, a summary is provided of the cost analysis, LYG, ICER per QALY and qualitative benefits for no screen vs. LDCT vs. EPISEEK. In order for EPISEEK to become preferable over LDCT, our research strongly suggests that coverage or reimbursement from third party payers such as Medicare or Medicaid will warrant precedence over annual LDCT.

screening method	direct out-of-pocket cost	LYs gained	ICER per QALY	qualitative benefits
no screen	$0	n/a	n/a	- *No risk of false positives* - *No incidental radiation* - *Convenient in pre-symptomatic stages*
LDCT	$300-500	0.0316	$49,200-$81,000	- *Covered for high-risk individuals by most insurers* - *Established method recommended by USPSTF and CMS*
EPISEEK	$699	0.0316†	$49,200-$81,000†	- *Available directly to consumers* - *Lower productivity and administrative cost burden: blood draws are more convenient for both patient and provider than CT scans* - *Reduced personnel cost: does not require interpretation by radiologist* - *Competitively-priced MCED: screens for multiple solid tumors, including lung, breast, prostate, and colorectal cancers, in addition to cancers that do not currently have any recommended screens (e.g. pancreatic)* - *Avoids false positives in patients with fungal cocci (Valley Fever)*

Table LC1: A summary comparison of three screening methods based on available data. ICERs were based on a willingness-to-pay threshold of $100,000/QALY. †Pending further data, health utility values for EPISEEK are presumed to be similar to those for LDCT; values here reflect ranges determined by previous studies (Black *et al.*, 2014; Criss *et al.*, 2019).

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Appendix:

Acronym List:

ALA: American Lung Association

Bp-base pairs

CAD- Computer Aided Diagnostics

CDRH -Center for Devices and Radiological Health

CDC: Centers for Disease Control and Prevention

CED- coverage with evidence development

cfDNA: Cell-free DNA

CLIA- Clinical Laboratory Improvements Amendments

CMS- Centers for Medicare and Medicaid Services

CpG: Cytosine and Guanine dinucleotide

CSRN- Cancer Screening Research Network

CT- Computed Tomography

CTC: Circulating Tumor Cells

DCP- Division of Cancer Prevention

DNA: Deoxyribonucleic acid

DL- Deep Learning

EGFR- Epidermal growth factor

EMR- Electronic Medical Record

FDA- Food and Drug Administration

HHS- Human Health Services

HRU- Healthcare resource utilization

ICER- incremental cost-effectiveness ratios

IDE- Investigational Device Exemption

I-ELCAP- International Early Lung Cancer Action Program

IVD- In-vitro diagnostics

LDT- Laboratory Developed Test

LY- Life Years

LDCT: Low-dose Computed Tomography

MCED- Multi-cancer early detection

MRD- Minimal residual disease

NCD-national coverage determination

NCI: National Cancer Institute

NELSON- Nederlands-Leuvens Longkanker Screenings Onderzoek Trial

NGS- Next Generation Sequencing

NIH- National Institute of Health

NLST- National Lung Screening Trial

NSCLC: non-small cell carcinoma

NY-ELCAP -NY-Early Lung Cancer Action Project

OOP- Out-of-pocket

P.E.: Precision Epigenomics

PET CT- Positron Emission Tomography- Computed Tomography

PMA- Premarket Approval

PMD: Partially methylated domains

PPACA-Patient Protection and Affordable Care Act

PPPM- Per person per month

QALY-quality adjusted life years

qPCR-quantitative polymerase chain reaction

REACH- Real-world Evidence to Advance Multi-Cancer Early Detection Health Equity

SCLC: small cell lung carcinoma

SEER- Surveillance Epidemiology and End Results

SES- socioeconomic status

SoC- Standard of Care

TCET- Transitional Coverage for Emerging Technologies

TSG: Tumor suppressor genes

USPSTF- United States Preventative Service Task Force

Who: World Health Organization